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EXPERIMENTS ON THE BILIARY SECRETION OF THE DOG[1].

By WILLIAM RUTHERFORD, M.D., F.R.S., *Professor of the Institutes of Medicine in the University of Edinburgh, and* M. VIGNAL.

(From the Physiological Laboratory of the University of Edinburgh).

FIRST SERIES.

INTRODUCTION.

THE influence of mercury, podophylline, and taraxacum upon the biliary secretion of the dog was some years ago investigated by a committee, of which Professor Hughes Bennett was chairman and reporter. Dr Arthur Gamgee and Dr Rutherford were the two junior members of the committee, upon whom devolved the task of performing the experiments. On the recommendation of the committee, they resorted to the method of establishing permanent biliary fistulæ in dogs by occluding the common bile-duct, and establishing a communication between the fundus of the gall-bladder and the exterior of the abdomen. After the wound in the abdominal wall had completely healed, and nothing remained but the fistulous opening into the gall-bladder, through which all the bile secreted was necessarily discharged, a cannula was constantly kept in the fistula, and the bile collected in a large sponge placed in a tin box and secured to the abdomen of the animal. The dogs were kept on a fixed diet, so that any alteration in the amount or in the composition of the bile might not be due to a change in the food. Very great difficulty was experienced in making a constant collection of the bile extending over a number of days, and, notwithstanding the greatest care, it was repeatedly observed that remarkable variations took place in the amount of bile secreted daily when no cause could be assigned. This fact rendered the method of experiment then employed one from which it was difficult to arrive at just conclusions; nevertheless the experiments seemed to warrant the conclusion that "spontaneous diarrhœa, dysentery and purgation produced by pilula hydrargyri, calomel, corrosive sublimate, and prodophylline, diminished the solid constituents of the bile, and, with one exception, the fluid portion of the bile also" (*British Association Report*, 1868, p. 229). The method of experiment resorted to was essentially that which had been previously used by Scott and by Kölliker in similar researches; it was certainly a crude method, and we have no doubt that the one which we have had recourse to in the following research is much more fitted to give a reliable and decisive answer regarding the action of substances on the biliary secretion.

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[1] Reprinted from the *Journal of Anatomy and Physiology*.

Two years ago, Röhrig (*Experimentelle Untersuchungen über die Physiologie der Gallenabsonderungen*, Stricker's *Jahrbücher*, 1873, p. 240) performed a number of experiments on the effect of various substances on the biliary secretion. He observed the rate of the biliary flow from temporary fistulæ in fasting curarised animals before and after the injection of purgative agents into the stomach and intestine. He found that large doses of croton oil greatly increased the secretion of bile, and that a similar effect, though to a less extent, was produced by colocynth, jalap, aloes, rhubarb and senna, and sulphate of magnesia—the potency of these agents as hepatic stimulants being in the order mentioned. He found, moreover, that castor-oil had little effect, and that calomel, while it seldom re-called the biliary secretion after it had ceased, nevertheless somewhat augmented it when it was taking place slowly.

Röhrig's statement with regard to calomel does not much differ from that made by Hughes Bennett's committee, and he made no experiments with podophylline and taraxacum; nevertheless, he did find that certain purgative agents, when given to *fasting* animals with temporary biliary fistulæ, increased the biliary secretion, while the committee found that in *non-fasting* animals with permanent fistulæ, purgative action induced by podophylline, calomel, etc., diminished the amount of bile secreted in the twenty-four hours.

It appeared to the reporter that this important subject should not be allowed to remain in its present position: ac-

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cordingly, he undertook the following research, and invited the co-operation of Monsieur Vignal, who had come to work in his laboratory.

METHOD OF EXPERIMENT.

All our experiments were performed on dogs,—these being the only available animals suitable for the purpose. They had always a full meal of flesh at four o'clock in the afternoon, and the experiment was begun between nine and ten o'clock on the following morning, so that digestion and absorption had fully taken place;—a condition that is essential for obtaining a constant secretion of bile. After paralysing the animal with curara, and establishing artificial respiration, we opened the abdomen in the linea alba, and tied a glass cannula in the common bile-duct, near its junction with the duodenum. To the end of the cannula which projected from the abdomen we attached a short India-rubber tube, and to the end of this again a short tube of glass, drawn to a narrow aperture, so that the bile might drop from it. The gall-bladder was then compressed, in order to fill the whole tubing with bile, and the cystic duct was clamped to prevent the return of the bile to the gall-bladder, and so compel all the bile secreted by the liver to flow through the cannula. The wound in the abdominal wall was then carefully closed; and in all our later experiments the animal was thoroughly covered with cotton-wool, in order to quickly restore it to its normal temperature.

Röhrig estimated the velocity of the biliary secretion by counting the seconds that elapse between the fall of the drops from the orifice of the tube. A single trial convinced us that this method is extremely laborious, and by no means accurate, seeing that it does not permit of continuous observation for any length of time. Moreover, we saw that the degree of viscosity of the bile caused a variation in the size of the drops, and, therefore, in the intervals between their fall. We therefore abandoned this for the more accurate method of allowing the bile to flow into a fine cubic centimeter measure, and recording the quantity secreted every quarter of an hour. In addition to constant collection of the bile, this method has the great advantage of permitting a graphic representation of the results. We, moreover, took the trouble to analyse the bile in many cases, and to make *post-mortem* examinations of the alimentary canal; points entirely omitted by Röhrig, but which, nevertheless, have yielded valuable results.

Until it is attempted, one might suppose that this mode of experiment is extremely simple, but it is by no means so simple as it appears. It is needful to manipulate the abdominal viscera with great care, and to avoid all dragging at the bile-duct, otherwise the secretion of bile becomes so irregular that the experiment may be useless. The cannula must be very carefully retained in a position which will permit of its moving with the diaphragm, but will prevent it from twisting the duct, and thus impeding the exit of the bile by forming a valve at its orifice.

The respiration requires to be maintained with regularity, otherwise the biliary flow is rendered somewhat unequal by irregular diaphragmatic compression of the liver. Moreover, if the respiration be deficient, the secretion of bile is always diminished (Röhrig). Some of the slight oscillations observable in the charts of the biliary secretion in these experiments are probably owing to variations in the respiration; for in the earlier experiments we were obliged to have the respiratory bellows moved by the hand, and this is never so regular as a machine. Notwithstanding this, however, the main results of these experiments are perfectly clear.

It is essential that the fall of temperature which follows the opening of the abdominal cavity be speedily overcome, otherwise the biliary secretion may be abnormally low at the outset of the experiment. For this purpose the animal was covered with cotton wool as above stated.

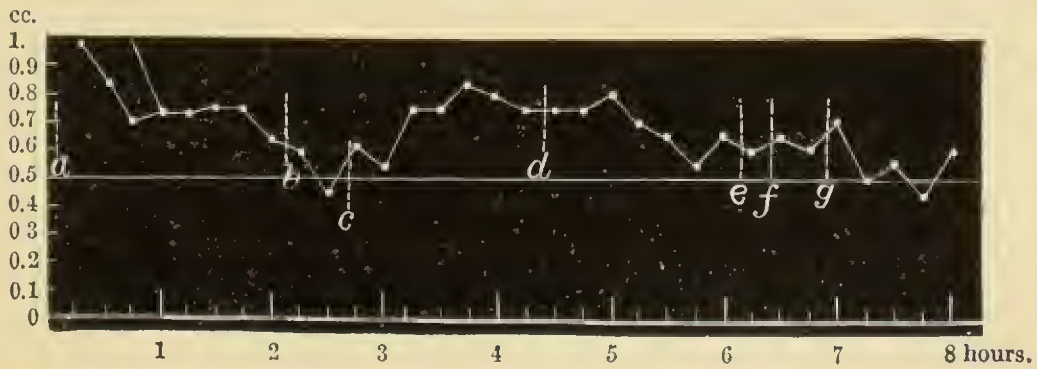
SECRETION OF BILE IN A CURARISED FASTING DOG.

It was of course necessary—as a preliminary step—to observe the amount of bile secreted in the course of a day by a dog that had fasted about eighteen hours, and to which nothing but curara was administered. The solution of curara employed in all the experiments was a filtered aqueous solution, every minim of which contained one milligramme of the poison. The solution was always injected into the jugular vein.

In all the illustrations the numbers under the horizontal line indicate the hours during which the secretion of bile was observed, while those to the left of the vertical line indicate in cubic centimeters the amount of bile which flowed from the cannula; the dots in the curve indicate the quantities of bile collected every quarter of an hour. The vertical dotted lines that cross the curves in the illustrations indicate that something was given to the animal. In all such experiments the amount of bile first collected is usually much greater than that at subsequent periods. This apparently results from the sudden diminution in the resistance to the exit of the bile which follows the opening of the duct. The first one or two collections are therefore not reliable indices of secretion, and they are consequently omitted from some of the charts.

Experiment 1. Dog that had fasted 18 hours. Weight 7.6 kilogrammes.—Twenty milligrammes of curara were injected into jugular vein (at *a*, Fig. 1). The abdomen was then opened, and the cannula placed in the common bile-duct, as above indicated. The wound in the abdomen was closed, the animal enveloped in cotton wadding, and the bile collected. As the experiment proceeded, the effect of the curara gradually wore off, owing to its elimination, and it was necessary to inject from two to four *milligrammes* from time to time (*b*, *c*, *d*, *e*, *f*, *g*, Fig. 1). If the curve be examined, it will be observed that these doses had no apparent effect on the biliary secretion, which was in this case tolerably regular. After falling until the middle of the third hour, it increased for a time and then fell somewhat. At the eighth hour it was slightly below what it had been at the close of the first.

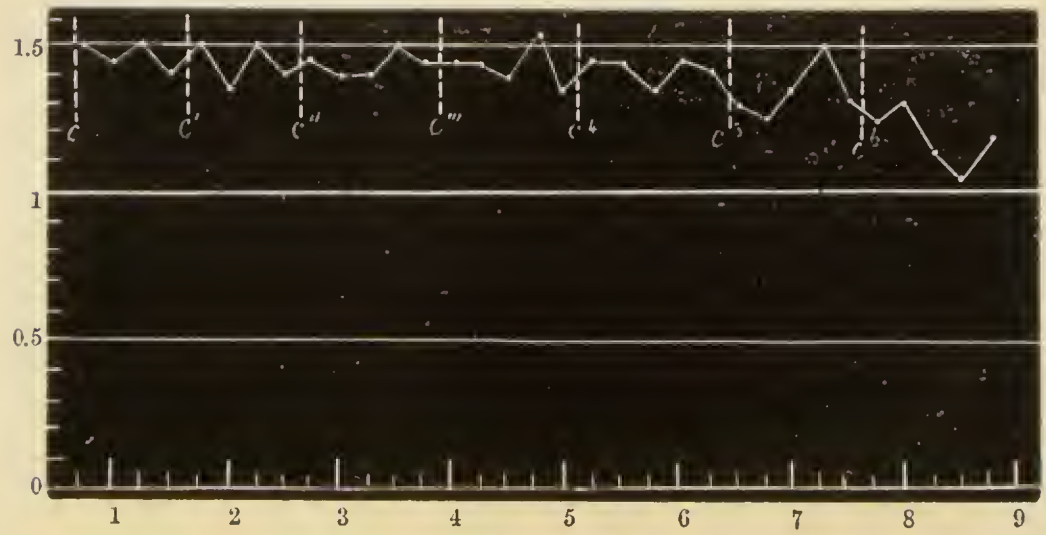
Fig. 1.



Secretion of bile by a fasting dog with nothing but curara administered. *a*. 20 mill.; *b*. 2 mill.; *c*. and *d*. 4 mill.; *e*, *f*, *g*. 3 mill. curara injected into jugular vein.

Experiment 1 A. Dog that had fasted 17 hours. Weight 18.7 kilogrammes. Fig. 1 A.

Fig. 1 A.



Secretion of bile by a fasting dog with nothing but curara administered. 20 mill. given at c, 4 mill. given at c', c'', c''', c^4, c^5, 3 mill. given at c^6.

As it is evident from these two experiments that doses of curara such as those given above do not apparently affect the biliary secretion, the times at which they were given are not indicated in any of the subsequent charts, for in all cases curara was given as above indicated. The great value of this substance in this connection is, that while not obviously affecting biliary secretion, as chloroform[1] and opium do, it—by paralysing voluntary movement—prevents the irregular outflow of the bile that ensues when the abdominal muscles contract.

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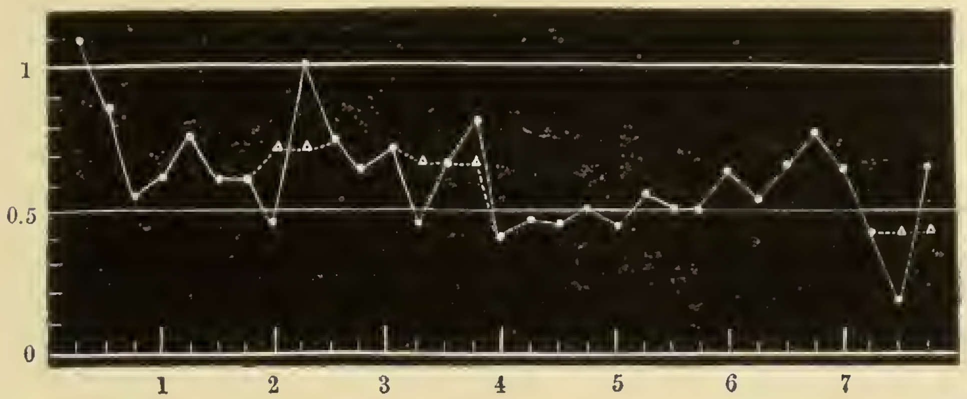
[1] Much surprise has been expressed by the ignorant that anæsthetics were not used in these experiments, at least during the preliminary operation required for the insertion of the cannula into the bile-duct. One reason for the omission is simply this, that we ascertained in two experiments, that *chloroform excites the liver so seriously that equivocal results could only be obtained by giving other cholagogues after it.* Röhrig has shown that opium has a similar action. We therefore deemed it necessary to give nothing but curara for the purpose of keeping the animal motionless, seeing that, as explained, the doses of this substance above mentioned do not apparently affect the biliary secretion.

It may be well to state, however, that in the operations for the previous experiments on the action of cholagogues performed by Dr Rutherford nine years ago, at a time when there was no antiphysiological excitement prevailing, chloroform was fully administered to every animal, because in those experiments the biliary fistula was of a permanent nature, and observations were not begun on the biliary secretion until some days after the operation—when of course the effect of the chloroform had completely passed off. The biliary fistulæ being of a temporary character in the present research, and the whole time taken up by each experiment being not more than a few hours, an anæsthetic was inadmissible.

The analysis of the bile in such a case as the above having been omitted, another experiment was performed for the purpose of supplying the want.

Experiment 2. Dog that had fasted 19 hours. Weight 15 kilogrammes.—Nothing was given but curara in doses similar to those above mentioned.

Fig. 2.



Secretion of bile in a fasting dog with nothing but curara administered.

The biliary flow was not so regular in this as in the previous cases. The mean has been taken, and triangles with dotted lines are superadded in the Fig. for the purpose of indicating the probable position of the *dots* had the secretion been regular. This was done on the supposition—entertained until more experience was gained—that these irregularities in the curve were due, not to variation in *secretion,* but to irregularity of *outflow,* owing to a variation in the facility with which the bile could enter the cannula. It was in time ascertained, however, that an irregular curve generally ensued when there was much difficulty in inserting the cannula into the duct, and the latter had to be a good deal pulled about; in consequence of which the liver probably suffered somewhat from nervous irritation.

Composition of Bile in a Fasting Dog.

Analyses were made of the bile secreted by the second dog during the first, fourth, and last hours of the experiment. The following are the results.

TABLE I.—*Composition of Bile secreted by a Dog paralysed by Curara after fasting eighteen hours.*

Experiment 2.	Bile secreted during		
	First Hour.	Fourth Hour.	Last Hour.
Water	89.53	89.58	89.55
Bile-acids, pigments, cholesterin, fats	8.73	8.68	8.71
Mucus	0.71	0.72	0.72
Ash	1.03	1.02	1.02
Total	100.00	100.00	100.00

Experiment 1.		Experiment 1A.		Experiment 2.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
1.0		1.5		1.1	
0.85		1.47		0.85	
0.7		1.5		0.55	
0.75	0.394	1.4	0.307	0.6	0.17
0.75		1.5		0.75	
0.75		1.35		0.6	
0.75		1.5		0.6	
0.65	0.309	1.4	0.3	0.45	0.19
0.6		1.42		1.0	
0.45		1.4		0.75	
0.65		1.4		0.65	
0.55	0.381	1.5	0.312	0.7	0.177
0.75		1.47		0.45	
0.75		1.45		0.65	
0.85		1.42		0.8	
0.8	0.393	1.4	0.305	0.4	0.12
0.77		1.52		0.45	
0.77		1.37		0.45	
0.75		1.42		0.5	
0.8	0.355	1.42	0.301	0.45	0.133
0.7		1.37		0.55	
0.65		1.45		0.5	
0.55		1.4		0.5	
0.65	0.328	1.3	0.288	0.62	0.168
0.6		1.27		0.55	
0.65		1.32		0.6	
0.6		1.5		0.75	
0.7	0.292	1.3	0.267	0.65	0.123
0.5		1.25		0.4	
0.55		1.3		0.15	
0.47		1.15		0.65	
0.6		1.05			
	Mean.	1.2	*Mean.*		*Mean.*
	0.351 cc.		0.254 cc.		0.154 cc.

It therefore appears that in the progress of the experiment the composition of the bile remained almost precisely the same. This is remarkable, seeing that the animal had been deprived of water for so long a time, and, moreover, seeing that the entrance of the bile into the intestine had been cut off. It should be mentioned that in taking the bile secreted near the beginning of such experiments for analysis, we were always careful to eliminate that which had been expressed from the gall-bladder into the cannula.

SECRETION OF BILE PER KILOGRAMME WEIGHT OF A DOG IN A FASTING CONDITION.

The absolute quantity of bile secreted by different individuals varies with the size of the animal; therefore, in order to ascertain the amount of work that is really done by the liver in any case, it is necessary to know the quantity of bile secreted per kilogramme weight of the animal in a unit of time. In all these experiments, therefore, the animals were weighed, so that the secretion of bile per kilogramme might be determined.

In the three curara experiments detailed above, the mean secretion per kilogramme weight of the animal was 0.351 cc. in Exp. 1, 0.254 cc. in Exp. 1 A, and 0.154 cc. in Exp. 2. In the first case, the secretion was, from some unknown cause, unusually high: the last two figures will be found a much nearer indication of what is usual in the fasting animal, but in subsequent experiments it will be seen that the secretion is frequently below even the small figure in Exp. 2.

Undoubtedly, the true test of hepatic work is the amount of bile *solids* secreted per unit of animal weight, in a unit of time. Any one may calculate this from the analyses, but inasmuch as these were not made in every case, and seeing that we have found that whenever a substance increases the biliary secretion, it augments the excretion of bile-solids by the liver, even although the bile be rendered more watery, we have thought that a statement of the amount of *fluid bile* secreted per kilogramme of dog will be sufficiently refined for the purpose of this research, because the question we have set ourselves to answer is principally this: What substances have the power of exciting the secreting apparatus of the liver? a question which cannot be answered by the ordinary observations on man, for there it is impossible to determine whether an increased amount of biliary matter in the dejections is due (1) To contraction of the gall-bladder, and larger bile-ducts. (2) To the relief of some possible spasm of the larger bile-ducts, or (3) To an increased secretion by the liver.

A second question before us is the relative powers as hepatic stimulants of the various substances employed. Our answer to this can only be approximative, for it would require a considerable number of experiments with any one substance to ascertain the most effective dose in the dog. This would entail an amount of suffering and of labour that seems altogether unwarranted by the result to be attained. We therefore believe that we do enough if we give a definite answer to the first of our questions, and an approximative answer to the second. The latter will be fairly well given by determining the amount of bile secreted per kilogramme weight of the animal per hour.

ACTION OF CROTON OIL.

Röhrig has placed croton oil at the head of his list of hepatic stimulants, with the statement that in doses from eighteen drops to a "teasponful" it has an exciting effect on the biliary secretion even under the most unfavourable circumstances (*lib. cit.* p. 250). This substance was therefore made the subject of our first experiments with cholagogues.

Experiment 3. Dog weighing 7.3 kilogrammes.—Considering the small size of this dog, the secretion of bile was unusually great. This probably resulted from digestion being incomplete; for, although the animal was fed seventeen hours before the experiment, at death a quantity of elastic tissue, and a greyish fluid resembling chyme, were found in the stomach. After the secretion had fallen very low, fifteen grains (about thirty drops) of croton oil, in sixty minims of almond oil, were injected directly into the duodenum[1] (at *c*, Fig. 3). The dose was a large one, but not so large nor yet so small as the quantities given by Röhrig. After half-an-hour, the fall in the bile-secretion was arrested, and a slight rise took place. Towards the close of the experiment, the pulse became extremely weak.

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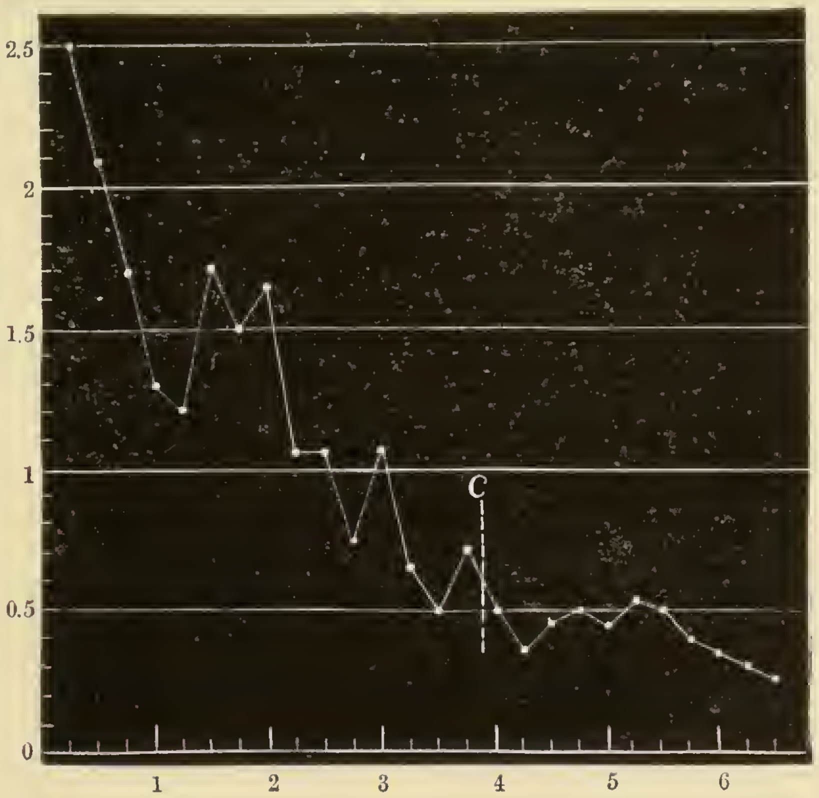
[1] In all cases the substances were injected into the duodenum, because the animals being curarised could not swallow, and the penetration of the duodenal

AUTOPSY[1].—The mucous membrane of the upper three-fourths of the small intestine was intensely red, especially in the duodenum, the colour of which resembled that of claret. There was evidence of impending purgation in the small intestine. The weak pulse at the close of this experiment,

Fig. 3.



Secretion of bile when digestion was incomplete. Fifteen grains croton oil injected into duodenum at *c*.

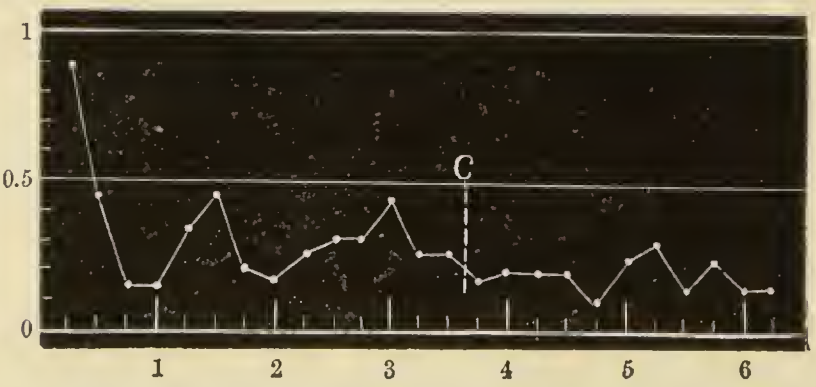
wall by the sharp nozzle of a syringe was a much simpler operation than the introduction of a tube down the œsophagus into the stomach. Moreover, the stomach in a dog that has fasted for many hours usually contains a large quantity of mucus that must have retarded the absorption of the substance if given by the mouth. To avoid this delay was a matter of great importance, both on the animal's account, and also because of the impossibility of continuing the experiment for more than a few hours. Moreover, it has been alleged that the action of a cholagogue may be due to a reflex excitement of the liver proceeding from the duodenal mucous membrane; therefore by always injecting the substances into the duodenum we ensured its action—if any—on this portion of the intestine.

[1] In all cases, unless otherwise stated, the autopsy was performed immediately at the close of the experiment.

together with the violent intestinal irritation, suggested that the collapse had been occasioned by the drug, and that a smaller dose should be given in the next experiment.

Experiment 4. Dog weighing 5.9 kilogrammes.—This animal had refused almost all food for nearly two days. Six grains of croton oil in sixty minims of almond oil were injected into the duodenum (*c.* Fig. 4). No increase of the biliary secretion followed. The pulse became so weak that the experiment was ended two hours and a half after the oil was given.

Fig. 4.



Secretion of bile before and after six grains of croton oil were injected into duodenum at *c*.

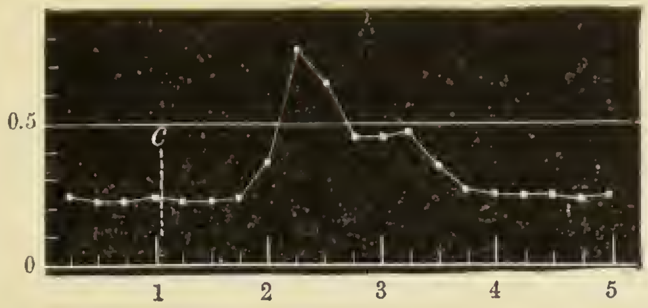
AUTOPSY.—The oil had found its way into the stomach. The gastric mucous membrane was of a claret colour. There was slight redness of the duodenum, but no evidence of purgative action.

Experiment 5. Dog that had fasted 18 hours. Weight 3.1 kilogrammes.—In this experiment, only three grains croton oil in sixty minims almond oil were injected into the duodenum. A decided increase in the biliary secretion began within an hour after the injection. The secretion soon reached a maximum, and then fell in the course of two hours to the same level as before the injection. (Fig. 5.)

AUTOPSY. A portion of the oil was found in the stomach, and another portion half way down the small intestine. The gastric mucous membrane was intensely red. There were patches of slight redness here and there in the duodenum. No evidence of purgative action.

These experiments were undertaken simply to test the accuracy of Röhrig's conclusion arrived at by his method of

Fig. 5.



The secretion of bile before and after three grains of croton oil were injected into the duodenum at *c*.

counting the drops of bile. Our method, which, as we have explained, is more reliable, gives no evidence that croton oil is to be regarded as a potent cholagogue, and, seeing that it has no reputation as such in practical medicine, we deemed further experimentation with it uncalled for.

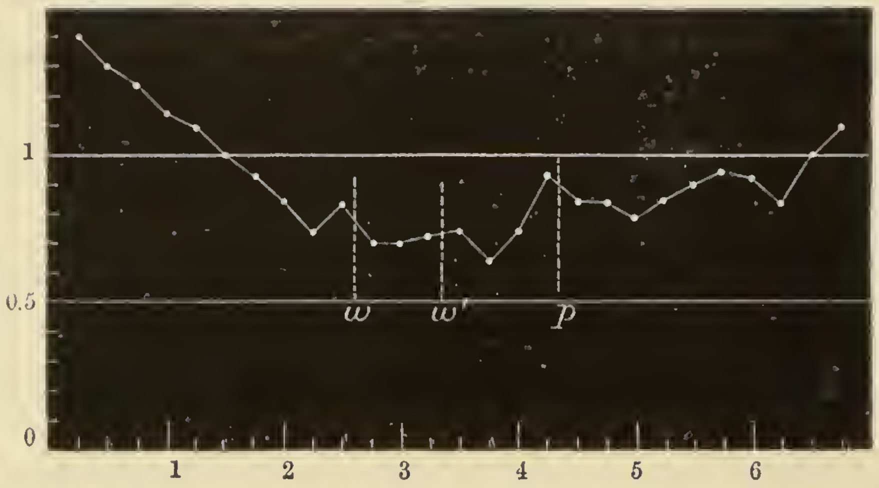
That there was no purgation from these doses of croton oil is a singular fact, which has been laid hold of by some persons as evidence that medicines affect the dog and man very differently, and that therefore the results seen in the one cannot be applied to the other. It is well known, however, that a difference in action is *quite exceptional*, and certainly the following experiments fully bear out this opinion. The only explanation of the non-purgative action of the oil in the above cases that suggests itself is that possibly too great a dose of this violent irritant was introduced into the intestine, and that a paralysis of Lieberkühn's follicles was the result. The large doses were given in imitation of Röhrig's experiments.

ACTION OF PODOPHYLLINE.

Experiment 6. Dog that had fasted 19 hours. Weight 15.3 kilogrammes.—The secretion of bile fell very gradually (Fig. 6). Ten cubic centimeters of water were injected into the duodenum at *w*. There being no apparent effect, 100 cc. were injected at *w'*. The slight rise in secretion that ensued at the end of an hour may have been owing to this; but it is not likely, seeing that water is absorbed with rapidity. At *p*, ten grains podophylline, suspended in 10 cc. water, were injected into the duodenum; and it is probable that the rise in secretion two hours afterwards was due to the podophylline.

Autopsy. The mucous membrane of the duodenum, and to a slight extent below it, was very vascular, and this part of the intestine contained a considerable quantity of a slightly brown fluid, thereby affording evidence of a purgative effect.

Fig. 6.

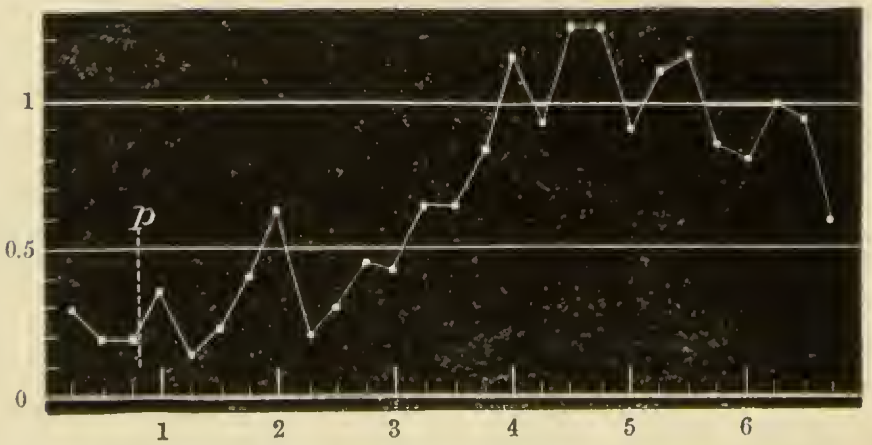


Secretion of bile before and after water and podophylline. *w*. 16 cc. water; *w′*. 100 cc. water; *p*. 10 grains resina podophylli in 10 cc. water injected into duodenum.

Experiment 7. Small dog that had fasted 19 hours.—Eight grains podophylline in 25 cc. water injected into duodenum (*p*. Fig. 7). The subsequent increase in the biliary secretion was most marked about four hours after administration, but by the end of the sixth hour the effect had greatly diminished.

Autopsy.—Upper part of small intestine contained a viscous brownish fluid. As the small quantity of water injected

Fig. 7.



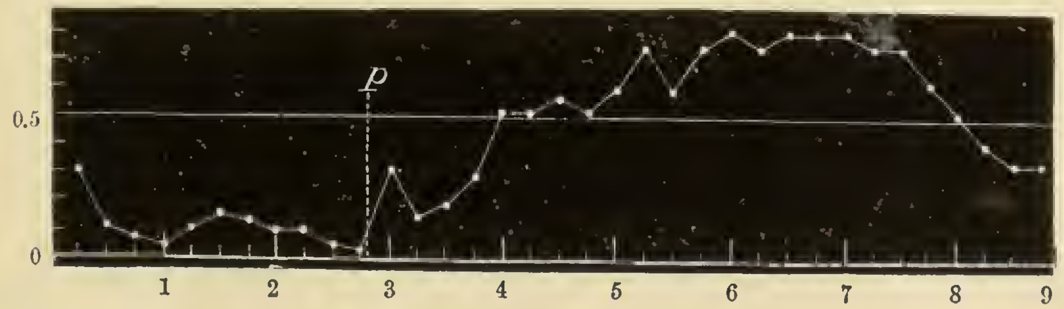
Secretion of bile before and after eight grains of resina podophylli in 25 cc. water were injected into duodenum at *p*.

had probably been absorbed, the intestinal contents were regarded as distinct, though not abundant, evidence of purgative action. The mucous membrane, to the extent of about eighteen inches below the pylorus, was extremely vascular. The remainder of the intestine was pale. A small quantity of mucus was found in the stomach, the mucous membrane of which was pale.

Experiment 8. Dog that had fasted 18 hours. Weight 6.6 kilogrammes.—Six grains podophylline in 9 cc. water injected into duodenum (*p*. Fig. 8). The subsequent rise in the bile-secretion is very evident. The secretion attained its maximum between three and four hours after the administration of the podophylline. As in the previous case, the effect on the liver had very greatly diminished by the end of the sixth hour after administration.

AUTOPSY.—Distinct, though not abundant, evidence of purgative action in small intestine, and decidedly increased vascularity of the mucous membrane in its upper two-thirds. Nothing remarkable in stomach or large intestine.

Fig. 8.

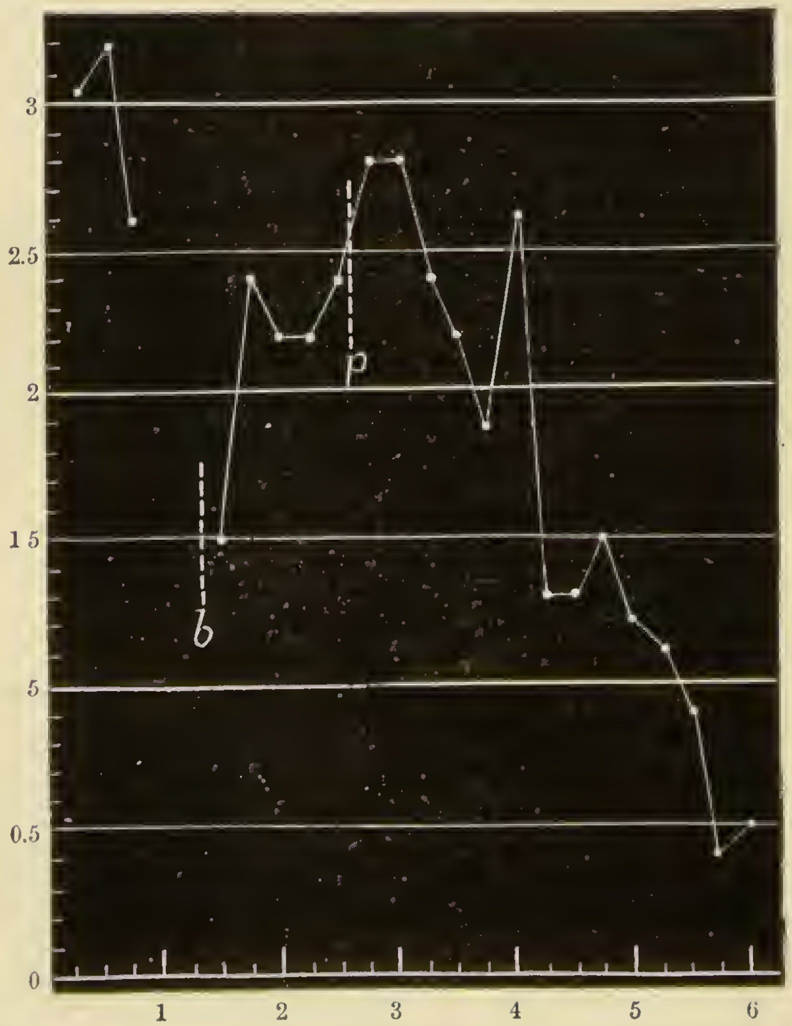


Secretion of bile before and after six grains of resina podophylli in 9 cc. water were injected into duodenum at *p*.

Probably every one will be struck by the slowness and the small extent of the purgative action in these experiments, notwithstanding the large doses of podophylline. That this was owing to the insolubility of podophylline in water is probable, from the two following experiments. Zwicke, Hagentorn, and Köhler having shown (Fraser's Report, *Journal of Anatomy and Physiology*, v. p. 393) that convolvulin, elaterin and some other substances have no purgative action unless they come in contact with bile—which, therefore, appears to be a solvent for them—it occurred to us that the tardy action of the podophylline might be owing to the non-entrance of the bile into the intestine. Accordingly, in the next experiment the podophylline was suspended in bile.

Experiment 9. Dog that had fasted 18 hours. Weight 11 kilogrammes.—12·2 cc. bile injected into duodenum (*b*, Fig, 9). Unfortunately, there is a hiatus in the curve immediately before the injection, owing to a loss of the bile; nevertheless it is evident that increased bile-secretion followed the injection when the biliary flow had become fairly constant. Nine grains podophylline, triturated in a mortar with 12 cc. bile, were injected into the duodenum (*p*). A rapid increase in the bile-secretion ensued; but it soon diminished, and three hours after the injection it was lower than it had ever been. In this remarkable experiment, therefore, the *diminution* of bile-

Fig. 9.



Secretion of bile before and after podophylline. *b*. 12.2 cc. bile; *p*. nine grains resina podophylli in 12 cc. bile injected into duodenum.

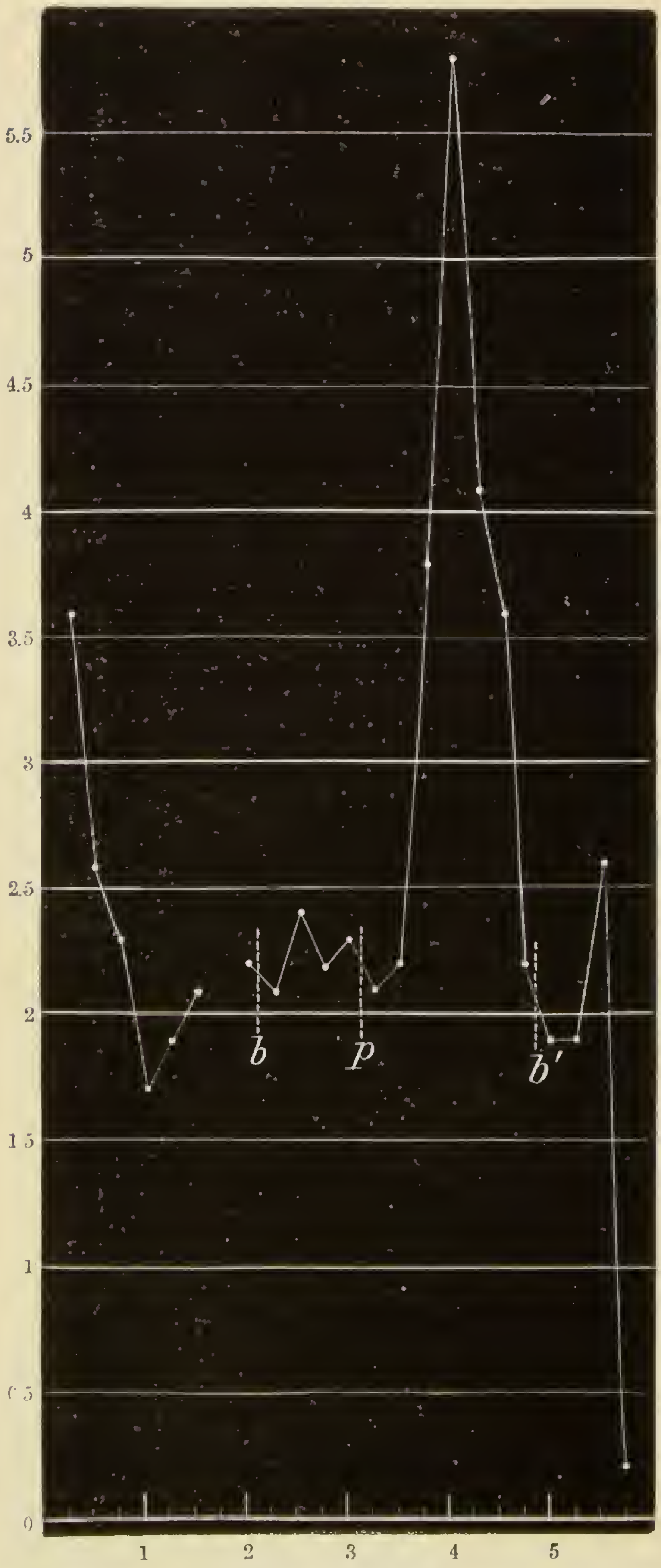
secretion after podophylline was far more remarkable than its increase; indeed, the increase might possibly have been owing to the injected bile, and not to the podophylline. Towards the close of the experiment the pulse became weak, but not excessively so.

AUTOPSY.—Mucous membrane of stomach and whole length of small intestine intensely red. The small intestine contained a large quantity of fluid. The large intestine contained a considerable quantity of liquid fæcal matters. There was, therefore, abundant evidence that excessive purgation was imminent.

In this experiment, the intestinal irritation and the purgative effect were far greater than they were in any of the previous experiments with podophylline, and it is evident that the principal change in the bile-secretion was *diminution.* It therefore appeared that, with a powerful solvent such as the bile, nine grains of podophylline produced a too violent effect upon the alimentary canal. The previous experiments having shown that, with a slighter action on the intestine, there was a more powerful action on the liver, suggested that with a smaller dose of podophylline given in the biliary solvent, an action on the liver would be evident, and that this would follow the injection more speedily than it had done in the experiments where the podophylline was not given in a state of solution. The next experiment realised this anticipation in a very striking manner.

Experiment 10. Dog that had fasted 19 hours. Weight 17.1 kilogrammes.—The bile-secretion was about 2 cc. per fifteen minutes before injection into the duodenum of 6 cc. bile and 6 cc. of water, *b*, Fig. 10. The subsequent increase of secretion was trivial. An hour after this, four grains podophylline, in the same quantity of bile and water, were injected (*p*). About half an hour afterwards a great acceleration of the biliary flow began, and lasted about an hour. In one of the periods of fifteen minutes, no less than 5.8 cc. of bile were secreted; a quantity never noticed in any other experiment, even on larger dogs. When this great hepatic excitement had disappeared, 6 cc. of bile and 6 cc. of water were again injected (*b′*), as in the first instance. The fall in the secretion was for a time arrested; but within three hours after the administration

Fig. 10.



Secretion of bile before and after podophylline. 6 cc. bile and 6 cc. water injected into duodenum at *b.* and *b′*. Four grains podophylline in the same fluids injected at *p*.

of the podophylline, the action of the liver had almost entirely ceased. The pulse was weak, but not extremely so.

AUTOPSY.—The mucous membrane of the duodenum was intensely vascular, but that of the remainder of the small intestine did not show an increased vascularity nearly so great as in the previous experiment. The upper three-fourths of the small intestine contained very decided evidence of purgative effect. The gastric mucous membrane had a dull red appearance.

Experiment 8.		Experiment 9.		Experiment 10.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
0.3		3.05		3.6	
0.1		3.2		2.6	
0.07		2.6		2.3	
0.05		lost.		1.7	
0.1		lost.		1.9	
0.15		*b* ——		2.1	
0.12		1.5		lost.	
0.1	0.042	2.4	0.836	2.2	
0.1		2.2		*b* ——	
0.05		2.2		2.1	0.526
0.03		2.4		2.4	
p ——		*p* ——		2.2	
0.32		2.8	0.927	2.3	
0.15		2.8		*p* ——	
0.2		2.4		2.1	
0.27		2.2		2.2	
0.52		1.9	0.645	3.8	1.01
0.52		2.6		5.8	
0.57		1.3		4.1	
0.52		1.3		3.6	
0.6		1.5	0.427	2.2	
0.75		1.2		*b′* ——	
0.6		1.1		1.9	
0.75		0.9		1.9	
0.8		0.4		2.6	
0.75	0.477	0.5		0.2	
0.8					
0.8					
0.8					
0.75					
0.75					
0.62					
0.52					
0.42					
0.35					
0.35					

Composition of Bile before and after Podophylline.

The next question to be answered was evidently this, is the increase in the quantity of bile after podophylline merely due to an increase of water, or are the bile-solids also increased? The bile secreted by dog 10, between the second hour and a half and the third hour, and that secreted an hour and a quarter after the administration of podophylline, were analysed with the following results. (Table II.)

Table II.—*Podophylline.*

Experiment 10.	Before.	After.
Water	90.83	91.07
Bile-acids, pigments, cholesterine, fats	7.75	7.84
Mucus	1.00	0.60
Ash	0.42	0.49
	100.00	100.00
Velocity of secretion per half-hour	4.6 cc.	9.6 cc.

It thus appears that, notwithstanding the great velocity of bile-formation, the special bile-solids were not diminished; the only noteworthy diminution being in the amount of mucus. This remarkable result was confirmed by the following analysis of the bile in another case. (Table III.)

Table III.—*Podophylline.*

Experiment 10 A.	Before.	After.
Water	94.26	94.28
Bile-acids, pigments, fats, cholesterine	4.66	4.68
Mucus	0.73	0.70
Ash	0.35	0.34
	100.00	100.00
Velocity of secretion per half-hour	1.86 cc.	2.47 cc.

Results of the Experiments with Podophylline.—1. Podophylline, when injected into the duodenum of a fasting dog, increases the *secretion* of bile. It is inferred that the increased biliary flow in the preceding experiments was due to increased *secretion*, and not merely to *expulsion*, because the gall-bladder had been wellnigh emptied by compression, and the cystic duct had been clamped: moreover, the increased flow was far too prolonged in some of the experiments to be attributable to spasm of the larger bile-ducts; therefore, an increase in secretion must have been the cause. 2. When the bile is prevented from entering the intestine, podophylline acts less powerfully and less quickly than when bile is introduced. 3. Augmentation of the biliary secretion is most marked when the purgative effect is not severe; indeed, if the purgative effect be very decided (*Experiment* 9), diminution and not augmentation of the biliary secretion may be the chief result. 4. Podophylline purgation is apparently due to a local action, for the irritation of the intestinal mucous membrane extends gradually from above downwards. 5. The bile secreted under the influence of podophylline, although it may be in increased quantity, contains as much of the special biliary matter as bile secreted under normal conditions.

These results are in exact accordance with clinical experience of the action of podophylline in man, but in addition they show that this substance actually increases the *secretion* of biliary matter, and that the liver is stimulated to secrete bile of the normal composition. They therefore supply information of a precise and important character, which the observations on the human subject have failed to give.

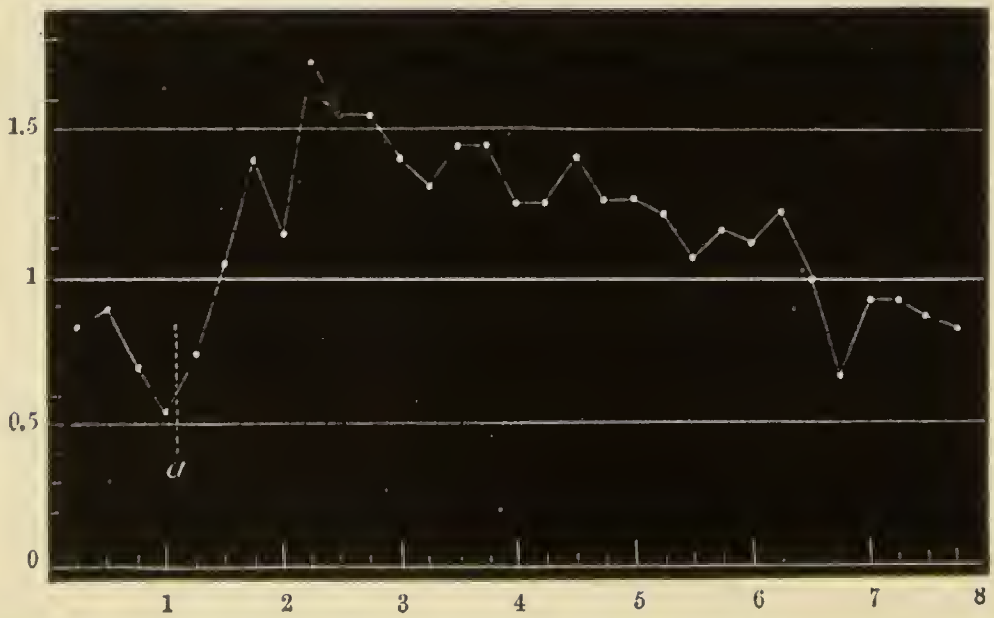
In the experiments with podophylline, performed by Hughes Bennett's committee above referred to, it was found that podophylline *diminishes* the secretion of bile. How is that statement to be reconciled with the above? The principal explanation is probably this, that in the experiments of the committee the doses given were large and generally produced *profuse purgation.* We see that in experiment 9 of this series diminished bile-secretion was the chief result of a dose that was too large, and it may be repeatedly observed in the following experiments. 1. That when a substance produces purgation, but does not stimulate the liver, it diminishes the secretion of bile. 2. That when a substance stimulates the liver as well as the intestinal glands, a moderate dose increases both the hepatic and the intestinal secretion, the effect on the former being most marked in the earlier part of the experiment, and diminishing as the purgative effect increases; but an excessive dose, by producing a violent purgative effect early in the experiment, may occasion nothing but diminished secretion of bile.

ACTION OF ALOES.

Although aloes has been found by Röhrig to accelerate the biliary secretion, we were anxious to compare its action, as ascertained by our method, with that of other substances; and we also desired to know the composition of the bile secreted before and after its administration.

Experiment 11. Dog that had fasted 18 hours, weight 8.6 kilogrammes.—Sixty grains of aqueous extract of Socotrine aloes in 12 cc. of water were injected into the duodenum (*a*, Fig. 11)[1]. A decided increase in the biliary secretion was perceptible within half-an-hour thereafter. After attaining a maximum about an hour and a half after the administration of

Fig. 11.



Secretion of bile before and after sixty grains extract of Socotrine aloes in 12 cc. water were injected into the duodenum at *a*.

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[1] This dose was probably much larger than need have been given, but when these earlier experiments were performed, we were under the impression that the dog requires larger doses than man. Further experience convinced us that this is exceptional. In many subsequent experiments we found that doses of various substances similar to those given to man act on the hepatic and intestinal glands of the dog.

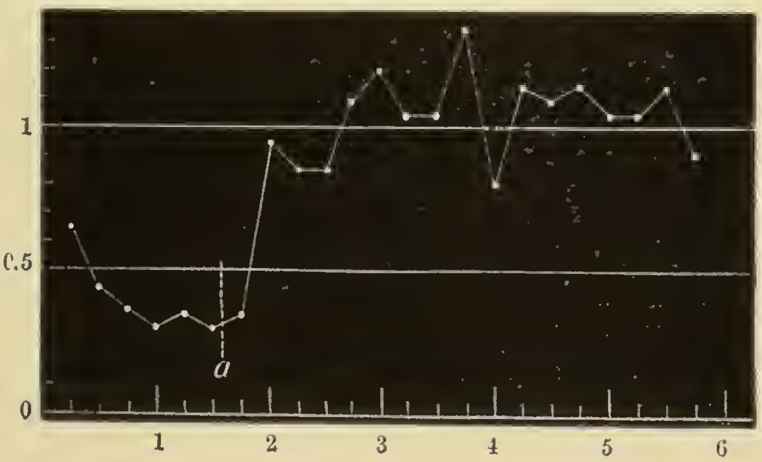
the drug, the secretion gradually fell; but although the experiment was continued for seven hours after the aloes was given, the effect had not disappeared.

AUTOPSY.—The aloes had extended along two-thirds of the small intestine, which contained about an ounce and a half of viscous fluid as the only evidence of purgation. There was a decided increase in the vascularity of the mucous membrane in this part of the intestine. The stomach contained a little mucus. Its mucous membrane was pale.

Experiment 12. Dog that had fasted 18 hours. Weight 5 kilogrammes.—Sixty grains of extract of Socotrine aloes in 12 cc. water were injected into the duodenum (at *a* Fig. 12). As in the previous experiment, the biliary secretion was increased within half an hour, and it became very strongly marked.

AUTOPSY.—The aloes had extended half way down the small intestine. This portion of the intestine contained about two ounces of viscous fluid; and its mucous membrane, together with that of the stomach, was intensely red.

Fig. 12.



Secretion of bile before and after sixty grains extract of Socotrine aloes in 12 cc. water were injected into the duodenum at *a*.

Composition of the Bile before and after Aloes.

It is evident from Tables IV. and V. that, under the influence of aloes, the bile became more watery; nevertheless, the amount of bile-solids secreted per unit of time increased.

TABLE IV.—*Aloes.*

Experiment 11.	Before.	After.
Water	84.11	91.44
Bile-acids, pigments, cholesterine, fats	12.45	7.53
Mucus	1.77	0.38
Ash	1.67	0.65
	100.00	100.00
Velocity of secretion per half-hour	1.5 cc.	2.65 cc.

TABLE V.—*Aloes.*

Experiment 12.	Before.	After.
Water	83.93	86.75
Bile-acids, pigments, cholesterine, fat	12.30	10.79
Mucus	2.74	1.49
Ash	1.03	0.97
	100.00	100.00
Velocity of secretion per half-hour	0.66 cc.	2.2 cc.

Results of Experiments with Aloes.—1. Sixty grains of the extract of Socotrine aloes, when placed in the duodenum, powerfully stimulated the liver. 2. Under its influence the liver excreted a greater quantity of biliary matter in a given time, although the bile was rendered more watery. 3. Coincident with the marked action on the liver there was only slight purgation.

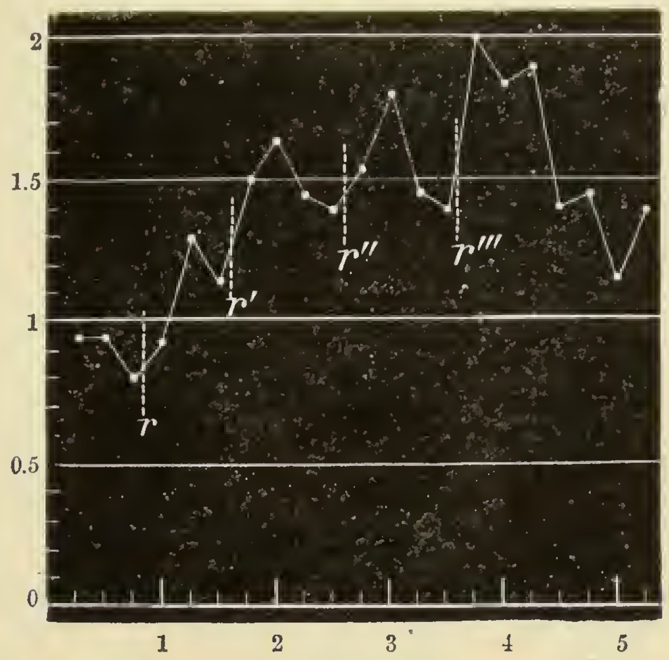
ACTION OF RHUBARB.

The following experiments show that rhubarb is also an undoubted hepatic stimulant. The ordinary infusion of the *British Pharmacopœia* was made with Indian rhubarb; it was then filtered and concentrated until 5 cc. contained the active part of seventeen grains of rhubarb. This was the dose employed.

Experiment 13. Dog that had fasted 15 hours. Weight 22·2 kilogrammes.—5 cc. of the above infusion of rhubarb were injected into the duodenum four times in succession

(r, r', r'', r''', Fig. 13). Within half-an-hour after every dose there was an increase in the biliary secretion.

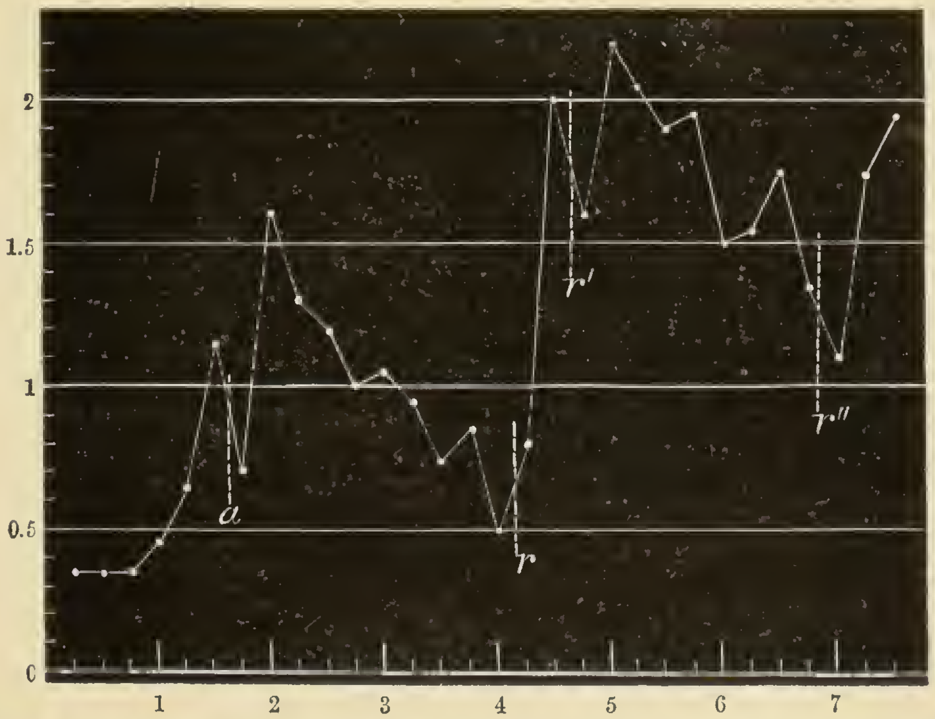
Fig. 13.



Secretion of bile before and after 5 cc. of a concentrated infusion of rhubarb were injected into duodenum at r, r', r'', r'''.

Autopsy.—The rhubarb had extended along about a third of the small intestine. There was no unusual redness of the

Fig. 14.



Secretion of bile before and after rhubarb. Artificial respiration improved at a. 5 cc. concentrated infusion of rhubarb injected into duodenum at r, r', and r''.

mucous membrane, and there was only slight evidence of purgative action.

Experiment 14. Dog that had fasted 18 hours. Weight 13.4 kilogrammes.—The artificial respiration, which was deficient at the commencement of this experiment, was improved at *a*, Fig. 14. This was followed by an increase in the secretion of short duration: 5 cc. of the same infusion of rhubarb as that used in the previous experiment were injected into the duodenum three times in succession (*r*, *r′*, *r″*, Fig. 14). The biliary secretion was augmented within half-an-hour after each injection.

AUTOPSY.—The rhubarb had extended along four-fifths of

Experiment 11.		Experiment 12.		Experiment 13.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
0.85	0.348	0.65		1.15	0.173
0.9		0.42		0.95	
0.7		0.37	0.264	0.95	
0.55		0.3		0.80	
a —		0.35		*r* —	
0.75		0.3		0.95	
1.05		*a* —		1.3	
1.4		0.35		1.15	
1.15	0.697	0.97		*r′* —	
1.75		0.87		1.5	0.27
1.55		0.85		1.65	
1.55		1.1		1.45	
1.4		1.2	0.93	1.4	
1.3		1.05		*r″* —	
1.45		1.05		1.55	0.279
1.45		1.35		1.8	
1.25		0.8		1.45	
1.25		1.15		1.4	
1.4		1.1		*r‴* —	
1.25		1.15		2.0	0.322
1.25		1.05		1.85	
1.2		1.05		1.9	
1.05		1.15		1.4	
1.15		0.9		1.45	
1.1				1.15	
1.2				1.4	
1.0					
0.65					
0.9					
0.9					
0.85					
0.8					

the small intestine. There was no unusual redness of the mucous membrane. The portion of intestine through which the rhubarb had extended contained 120 cc. of a thick yellowish fluid: there was, therefore, decided evidence of purgative action.

The amount of water given with the rhubarb in these experiments was so trivial that it may be entirely disregarded.

Composition of the Bile before and after Rhubarb.

TABLE VI.—*Rhubarb.*

Experiment 13.	Before.	After the second dose.	At the close of the experiment.
Water	88.80	89.28	88.98
Bile-acids, pigments, cholesterine, fat	9.60	9.60	9.60
Mucus	1.00	0.60	0.80
Ash	0.60	0.52	0.62
	100.00	100.00	100.00
Velocity of secretion per half-hour	1.9 cc.	2.95 cc.	2.55 cc.

TABLE VII.—*Rhubarb.*

Experiment 14.	Before.	After.
Water	85.47	86.23
Bile acids, pigments, cholesterine, fat	11.59	11.03
Mucus	1.87	1.72
Ash	1.07	1.02
	100.00	100.00
Velocity of secretion per half-hour	1.45 cc.	3.95 cc.

It therefore appears that rhubarb, like podophylline, excites the liver to secrete bile, having a composition similar to that secreted under normal conditions.

Results of Experiments with Rhubarb.—1. An infusion of seventeen grains of Indian rhubarb, when placed in the duodenum, never failed to increase the secretion of bile within half-an-hour after it was given. 2. The bile, although secreted in increased quantity, had the composition of normal bile as regards the biliary constituents proper. 3. The doses which excited the liver had in one case no marked purgative effect, but in another case the purgative effect was considerable.

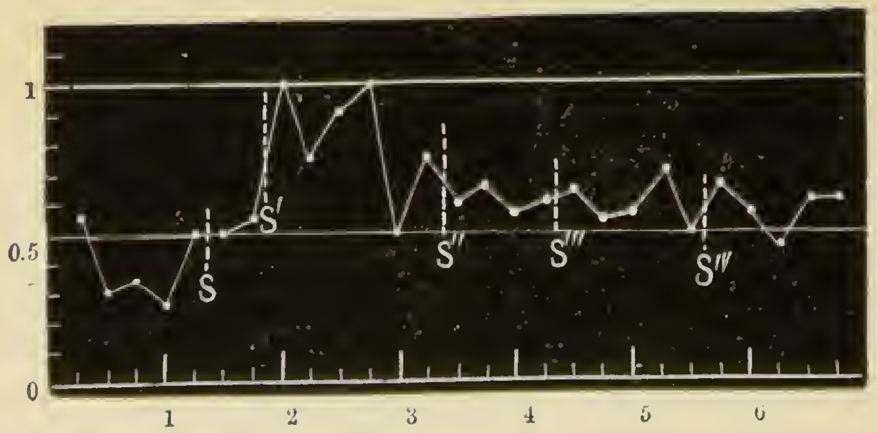
Notwithstanding the fact that rhubarb has been given to man for an indefinitely long period, there has always been considerable doubt as to its being a cholagogue, possibly because the colouring matter of the rhubarb increases the colour of the dejections in a manner similar to an increased discharge of bile. But by this method of investigation this source of fallacy is eliminated, and the action of rhubarb as a cholagogue proved in the case of the dog, and there seems no longer any reason to doubt that it has a similar action in man. If the amount of bile secreted per kilogramme of dog under the influence of rhubarb be compared with the results of the action of podophylline, it will be seen that rhubarb is a less powerful cholagogue; a conclusion that is quite in accordance with observations on man.

Action of Senna.

Senna excites the liver, but not so powerfully as rhubarb. The ordinary infusion of senna of the *British Pharmacopœia* was prepared and concentrated until 5 cc. contained the active part of forty-five grains of senna; a small dose for a man.

Experiment 15. Dog that had fasted 19 hours. Weight 8 kilogrammes.—5 cc. of the above-mentioned concentrated infusion of senna were injected into the duodenum five times in succession (s, s', s'', s''', s^{iv}, Fig. 15). The secretion of bile

Fig. 15.



Secretion of bile before and after senna. 5 cc. concentrated infusion of senna injected into duodenum at s, s', s'', s''', s^{iv}.

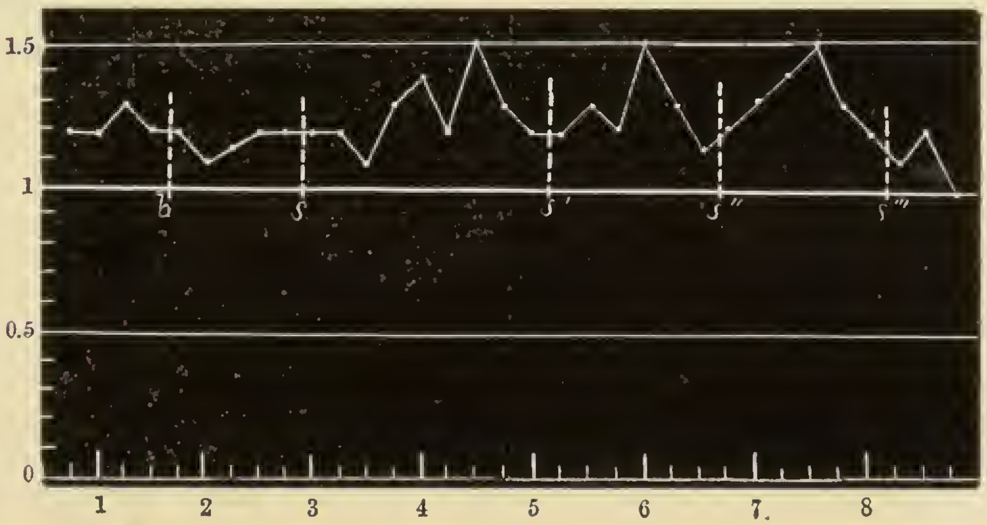
rose rapidly after the second dose, as in the previous experiment, but it soon fell again; and the third, fourth, and fifth doses did not increase it.

AUTOPSY.—The senna had extended along three-fourths of the small intestine, which contained 80 cc. of liquid. Seeing that the amount of fluid injected was 25 cc., considerable purgation had been produced. There was a considerable increase in the vascularity of the duodenal mucous membrane, but elsewhere there was no unusual redness.

Experiment 16.—Dog that had fasted 18 hours. Weight 23.1 kilogrammes.—$\frac{1}{2}$ cc. bile and 5 cc. water injected into duodenum at *e* (Fig. 16) and $\frac{1}{2}$ cc. bile with 5 cc. infusion of senna of the strength above mentioned were injected at *s*, *s′*, *s″*, *s‴*. There was only a slight increase in the biliary secretion.

AUTOPSY.—The senna had passed through the whole length of the small and had entered the large intestine. The amount of fluid in the small intestine was 103 cc., showing that a very considerable purgative effect had been produced.

Fig. 16.



Secretion of bile before and after senna. $\frac{1}{2}$ cc. bile and 5 cc. water injected. $\frac{1}{2}$ cc. bile and 5 cc. concentrated infusion of senna injected into duodenum at *s*, *s′*, *s″*, and *s‴*.

It appears from this analysis and from the velocity of secretion, that although senna causes the liver to excrete more biliary matter, its power is below that of rhubarb, as may be further seen by comparing the amount of bile secreted per kilogramme of dog, under the influence of senna and of rhubarb. It is extremely probable that the greater purgative influence of senna as compared with rhubarb is one cause of its less powerful action as a cholagogue (see p. 21).

Experiment 14.		Experiment 15.		Experiment 16.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
0.37		0.55		1.2	0.212
0.37		0.30	0.175	1.2	
0.35		0.35		1.3	
0.45		0.25		1.2	
0.65		0.5		e ——	
1.15		s ——		1.2	
0.7		0.5		1.1	
1.6		0.55		1.15	
1.3		s′ ——		1.2	
1.2		1.0	0.456	1.2	
1.0		0.75		s ——	
1.05		0.9		1.2	
0.95	0.227	1.0		1.2	
0.75		0.5		1.1	
0.85		0.75		1.3	
0.5		s″ ——		1.4	
r ——		0.6		1.2	
0.8		0.65		1.5	
2.0		0.55		1.3	
r′ ——		0.6		1.2	
1.6		s‴ ——		s′ ——	
2.2	0.604	0.62	0.298	1.2	
2.05		0.52		1.3	
1.9		0.55		1.2	
1.95		0.7		1.5	
1.5		0.5		1.3	
1.55		s^{iv} ——		1.17	
1.72		0.67		s″ ——	
1.37		0.55		1.2	
r″ ——		0.15		1.3	0.238
1.1		0.6		1.4	
1.75		0.6		1.5	
1.97				1.3	
				1.2	
				s‴ ——	
				1.1	
				1.2	
				1.0	

TABLE VIII.—*Senna.*

Experiment 15.	Before.	After.
Water	90.63	91.31
Bile-acids, pigments, cholesterine, fat	7.20	6.75
Mucus	1.30	1.20
Ash	0.87	0.74
	100.00	100.00
Velocity of secretion per half-hour	0.82 cc.	1.136 cc.

Results of the Experiments with Senna.—1. Senna is a hepatic stimulant of feeble power. 2. It renders the bile more watery.

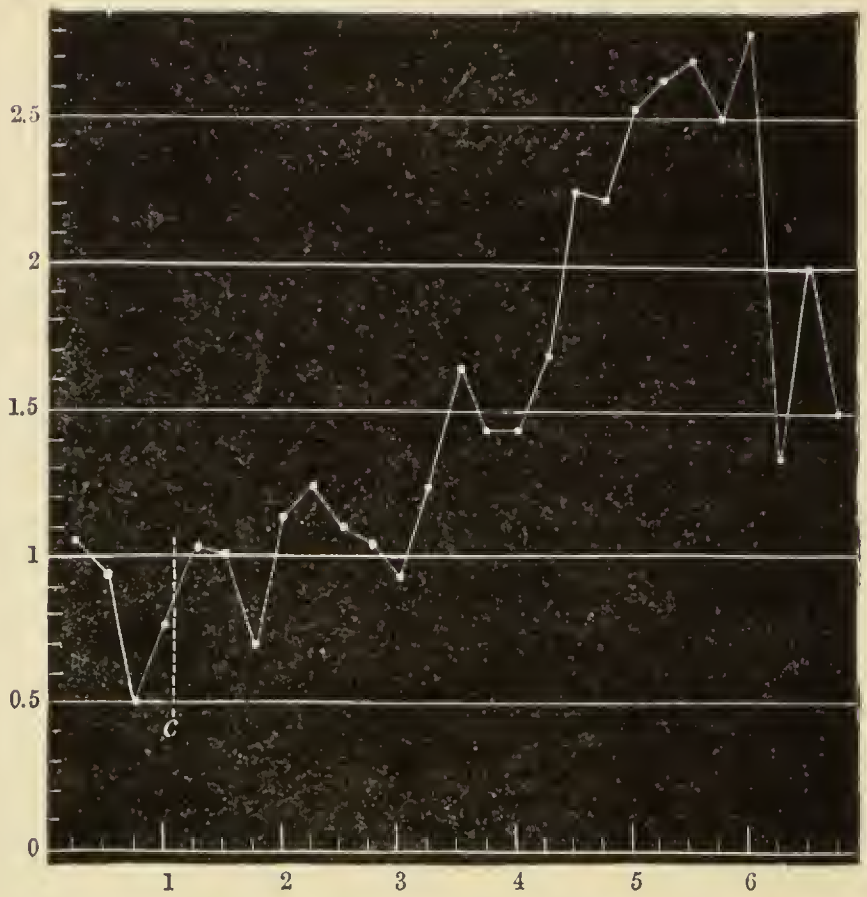
ACTION OF COLCHICUM.

Colchicum has been recommended as a cholagogue in cases of gout, but its action on the liver has not hitherto been tested by direct experiment.

Experiment 17. Dog that had fasted 16 hours. Weight 23.5 kilogrammes.—Sixty grains of the aqueous extract of colchicum of the *British Pharmacopœia* in 10 cc. of water were injected into the duodenum (*c*, Fig. 17). In an hour the biliary secretion began to increase, and five hours after the injection it was nearly five times more than before the drug was given. The secretion then fell, and just at the close of the experiment a large quantity of liquid fæces was discharged. The rise in the curve in Fig. 17 suggests a very powerful stimulation of the liver, but it must be remembered that the animal was of large size, and the table of numbers shows that the secretion per kilogramme of dog never went higher than 0.453 cc.

AUTOPSY.—There was great vascularity of the upper four-fifths of the mucous membrane of the small intestine. The vascularity of the duodenum was intense. The mucous membrane of the large intestine was also unusually vascular. The gastric mucous membrane was pale. There was evidence of considerable hydrocatharsis in the small intestine. The large intestine was empty, owing to the recent discharge of fæcal matter.

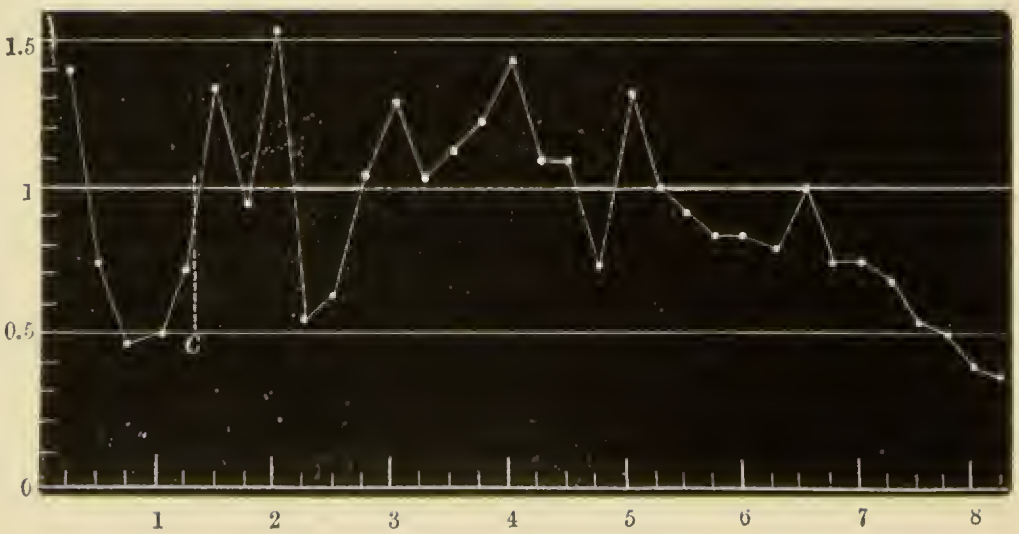
Fig. 17.



Secretion of bile before and after sixty grains extract of colchicum in 10 cc. water were injected into the duodenum at *c*.

Experiment 18.—Dog that had fasted 18 hours. Weight 23.6 kilogrammes.—Sixty grains of aqueous extract of colchicum in 10 cc. of water were injected into the duodenum (*c*, Fig. 18). Although the biliary flow thereafter varied much, a decided

Fig. 18.



Secretion of bile before and after sixty grains of aqueous extract of colchicum in 10 cc. of water were injected into duodenum at *c*.

increase was evident an hour and a half after the administration of the drug. The increase lasted about four hours, after which the secretion gradually fell. The liver was certainly excited, but not powerfully, for the secretion of bile per kilogramme of dog did not rise above 0.205 cc.

Autopsy.—There was increased vascularity of the mucous membrane of the upper three-fourths of the small intestine. The whole small intestine contained evidence of powerful cathartic action.

Experiment 17.		Experiment 18.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.
1.07	0.138	1.42	
0.92		0.75	0.1
0.5		0.47	
0.77		0.5	
c ——		0.72	
1.02	0.207	c ——	
1.0		1.35	0.186
0.7		0.95	
1.15		1.55	
1.25	0.227	0.55	
1.1		0.62	
1.05		1.02	
0.95		1.3	
1.25	0.216	1.02	0.205
1.65		1.15	
1.45		1.22	
1.45		1.47	
1.7	0.371	1.1	
2.25		1.1	
2.22		0.75	
2.55		1.35	
2.65	0.453	1.0	
2.7		0.95	
2.5		0.85	
2.8		0.85	
1.36		0.8	
2.0		1.0	
1.5		0.75	
		0.75	
		0.7	
		0.55	
		0.5	
		0.4	
		0.37	

These experiments show that the aqueous extract of colchicum in large doses increases the biliary secretion.

TABLE IX.—*Composition of the Bile before and after Colchicum.*

Experiment 18.	Before.	After.
Water	88.434	90.63
Organic Bile-solids	10.616	8.75
Ash	0.950	0.62
	100.00	100.00
Velocity of bile-secretion per half-hour	1.2 cc.	2.24 cc.

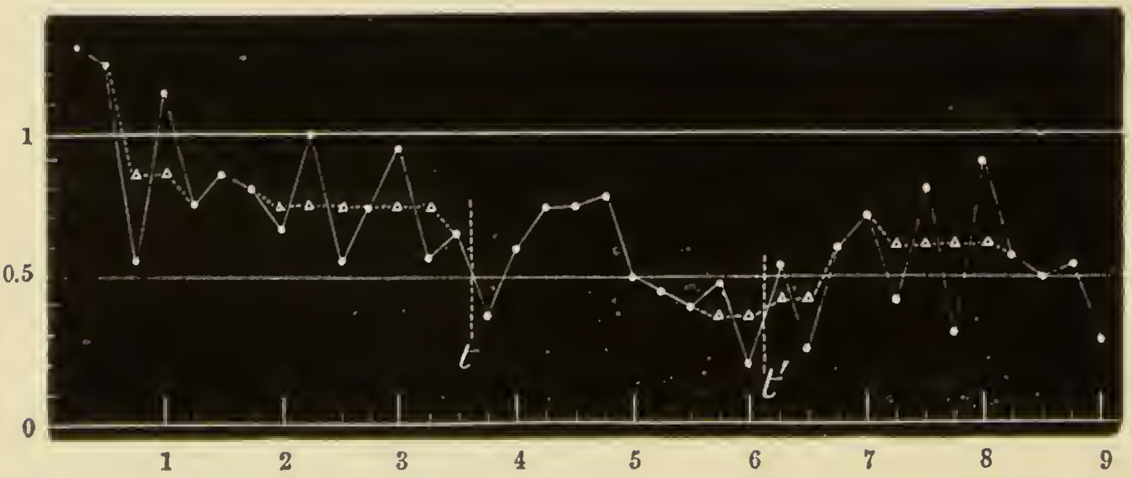
It appears from the above analysis that colchicum rendered the bile more watery; nevertheless, owing to the increased velocity of secretion, more biliary matter is excreted by the liver under under its influence.

Results of Experiments with Colchicum.—1. Sixty grains of the aqueous extract of colchicum powerfully excited the liver, and produced hydrocatharsis, although the absolute amount of bile secreted per kilogramme of dog was never very high. 2. Colchicum, although it increases the amount of biliary matter excreted by the liver, renders the bile more watery.

ACTION OF TARAXACUM.

Experiment 19. Middle-sized dog that had fasted 24 hours. —One hundred and eighty grains of solid extract of taraxacum in 25 cc. of water were injected into the duodenum (*t*, Fig. 19);

Fig. 19.



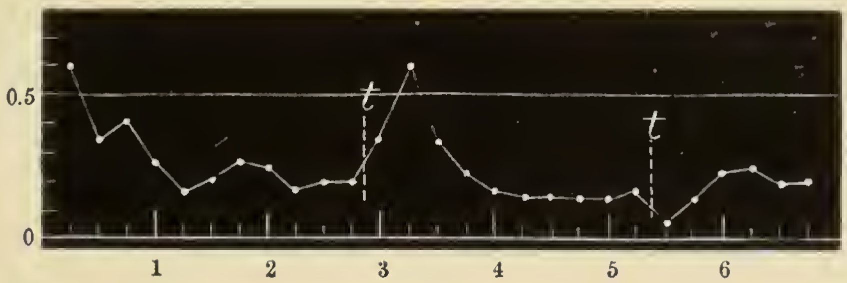
Secretion of bile before and after taraxacum. *t*, 180 grains; *t′*, 120 grains of solid extract of taraxacum in 25 cc. of water were injected into the duodenum. (The triangles and dotted lines indicate the *mean* of the high and low readings in order that a conclusion regarding the effect of the substance may be more easily arrived at.)

and two hours after this, one hundred and twenty grains in the same quantity of water were injected (*t'*). After both doses there was a greater increase in the biliary secretion than was at all likely to have been caused by the same quantity of water. (See *Experiment* 6.)

AUTOPSY.—The taraxacum had passed along nearly the whole length of the small intestine. Most of the fluid had been absorbed. There was no evidence of purgative action.

Experiment 20. Small dog that had fasted 18 hours.—One hundred and twenty grains of solid extract of taraxacum in 15 cc. of water were injected into the duodenum (*t*, Fig. 20), and this dose was repeated in two-and-a-half hours. The increase of the biliary secretion after the second dose was trivial; but after the first it was considerable, though of short duration. An examination of the intestine at death revealed no purgative action.

Fig. 20.



Secretion of bile before and after taraxacum. 120 grains of solid extract of taraxacum in 15 cc. of water injected into the duodenum at *t* and *t'*.

From these experiments it may be concluded that taraxacum is a very feeble hepatic stimulant, a conclusion that is in harmony with clinical experience, although the observations on man—from the nature of the case—have yielded nothing perfectly definite. We think it unnecessary to detail these two experiments more fully.

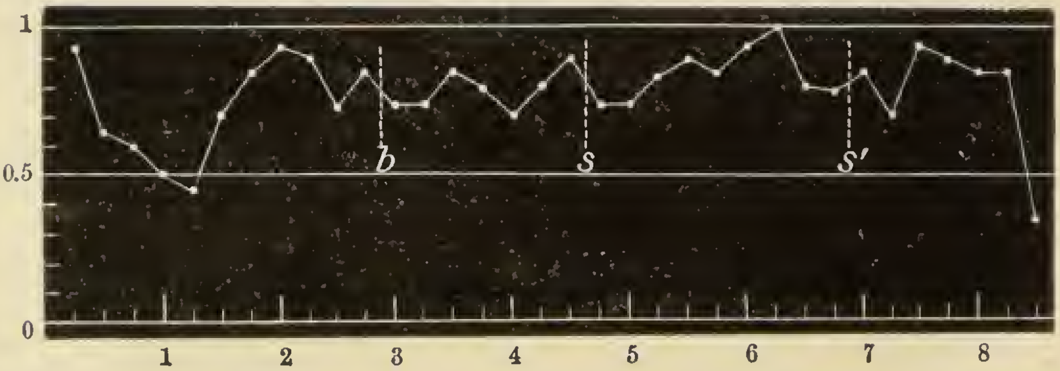
ACTION OF SCAMMONY.

The resin of scammony, being insoluble in water, was dissolved in dilute alcohol, and some bile was added, in order still further to promote its absorption from the alimentary canal.

Experiment 21. Dog that had fasted 18 hours. Weight 9.5 kilogrammes.—2.5 cc. bile were injected into the duodenum (*b*, Fig. 28). This produced no notable effect. Twenty grains of scammony resin were dissolved in 3.5 cc. rectified spirit, 3 cc. water and 3 cc. bile were then injected (*s*), and this dose was afterwards repeated (*s*′). There was a slight increase in the biliary secretion.

AUTOPSY.—There was greatly increased vascularity of the mucous membrane of the whole length of the small intestine. Vascularity of the gastric mucous membrane was also somewhat increased. There was evidence of severe purgative action in the whole extent of both the small and large intestine.

Fig. 21.

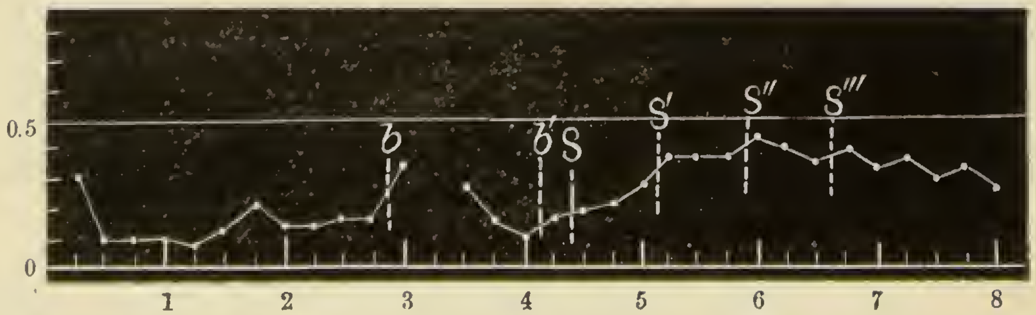


Secretion of bile before and after scammony. Bile injected into duodenum at *b*, and scammony with bile and alcohol at *s* and *s*′. (See text.)

Experiment 22. Dog that had fasted 19 hours. Weight 6.8 kilogrammes.—In this experiment it was determined to give scammony in smaller doses; 1 cc. bile and 2 cc. water were injected into the duodenum at *b*, Fig. 22.

The exact effect of this was not ascertained, owing to the loss of the bile secreted during one of the periods. About an hour after this, 0.25 cc. bile, 0.5 cc. rectified spirit, and 1.25 cc. water, were injected (*b*′). This having scarcely any effect, it was given with four grains of scammony resin at *s*, and again

Fig. 22.



Secretion of bile before and after scammony. Bile given at *b* and *b*′; scammony, etc., given at *s*, *s*′, *s*″, *s*‴.

at s'. The amount of scammony was doubled, and this dose was given at s'' and s'''. There was an increase of the biliary secretion after the first two doses of scammony, but after the third and fourth the secretion diminished.

As two experiments, not here reported, in which alcohol only was given, proved that it certainly does not augment the biliary secretion, this experiment shows that scammony is a hepatic stimulant, although not a powerful one.

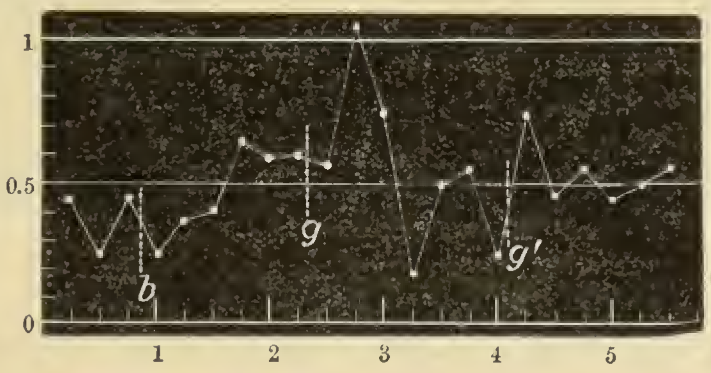
AUTOPSY.—The scammony had passed along two-thirds of the small intestine. There was decided evidence of purgation, but no remarkable increase in the vascularity of the mucous membrane.

From these experiments it appears that scammony is a cholagogue of feeble power, and it seems unnecessary to detail them further.

ACTION OF GAMBOGE.

Experiment 23. Dog that had fasted 18 hours. Weight 4.8 kilogrammes.—3 cc. of bile and 3 cc. of water were injected into the duodenum at *b* (Fig. 23). Previously to this there was, considering the small size of the dog, a large secretion of bile. The increased secretion which followed the injection was probably owing to the action of the bile. Twenty grains of gamboge in the same quantity of bile and water were given at *g*, and forty grains in the same fluid at *g'*. Half an hour after the first dose there was a decided acceleration of the biliary

Fig. 23.



Secretion of bile before and after gamboge. 3 cc. bile and 3 cc. water injected into duodenum at *b*; twenty grains gamboge at *g*, and forty grains at *g'*, in the same fluid injected into duodenum.

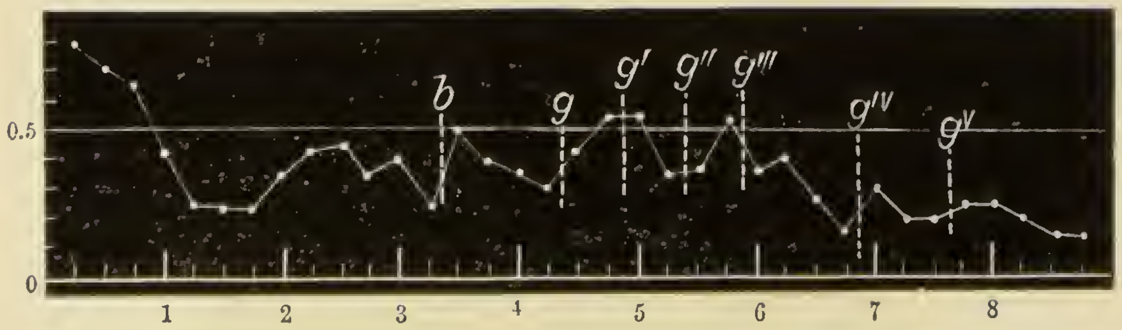
flow, but in an hour afterwards it had temporarily sunk nearly to zero. If the mean be taken, it will be found that the increase of secretion was so slight that it might have been due to the bile that was given with the gamboge. On the whole, therefore, it can scarcely be said that the amount of bile secreted was increased by the gamboge, and certainly the next experiment lent no support to such a view of the matter.

AUTOPSY.—There was great redness of the mucous membrane in the upper half of the small intestine. There was evidence of profuse hydrocatharsis in this portion of the gut. Some of the gamboge had passed into the stomach, the mucous membrane of which was somewhat reddened.

Experiment 24. Dog that had fasted 19 hours. Weight 8 kilogrammes.—1 cc. of bile and 2 cc. of water were injected into the duodenum at *b* (Fig. 24); four grains of gamboge in 0.2 cc. of bile and 2 cc. of water were injected at g, g', and g''. At g''', g^{iv}, g^{v}, twice the amount of gamboge was given in the same fluid. The increase in the bile-secretion after the first dose was trifling. The chief result of the experiment was *diminution* of the secretion.

AUTOPSY.—There was profuse hydrocatharsis in the small intestine. There was no very noteworthy increase in the vascularity of the mucous membrane.

Fig. 24.



Secretion of bile before and after gamboge. (See text.)

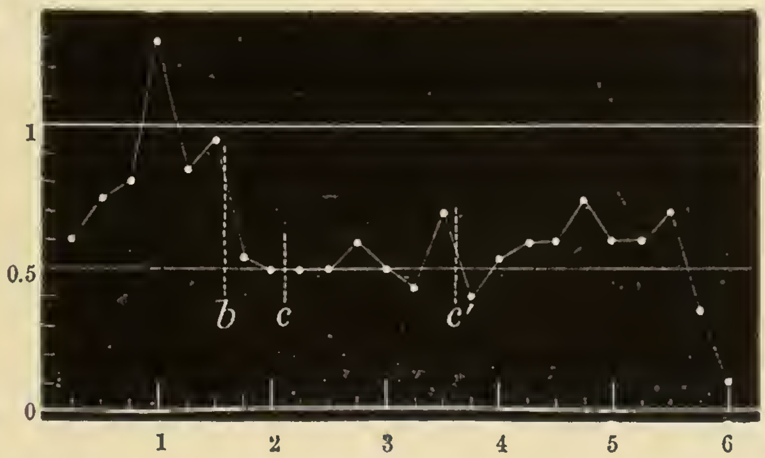
In Experiment 24, a smaller quantity of bile was given than in Experiment 23, in order to eliminate, as far as possible, its stimulating effect on the liver: 24 is therefore a better experiment than 23, and it affords no sufficient evidence that gamboge is a hepatic stimulant. It is thought unnecessary to detail the experiments on gamboge further. It is, however, extremely interesting to contrast the negative effect on the liver of this hydrocathartic with the positive effect of colchicum, also a hydrocathartic. In both there was violent irritation of the mucous membrane of the duodenum and small intestine generally. And it is important to observe that in the case of gamboge this irritation gave rise to no increased action of the liver, showing that duodenal irritation is not of necessity followed by hepatic excitement.

ACTION OF CASTOR-OIL.

Röhrig found that castor-oil has scarcely any effect on the hepatic secretion. It appeared, however, desirable to emulsify the oil with bile, so that its condition in the intestine might more closely resemble that in any normal case.

Experiment 25. Dog that has fasted 18 hours. Weight 7.7 kilogrammes.—3 cc. of bile were injected into the duodenum at *b* (Fig. 25). One ounce of castor-oil, emulsified with 3 cc. of bile, was injected into the duodenum at *c*, and again at *c′*. A slight increase in the bile-secretion followed the second dose; but as its extent was trifling, it should probably be disregarded. There was a great diminution towards the close of the experiment.

Fig. 25.



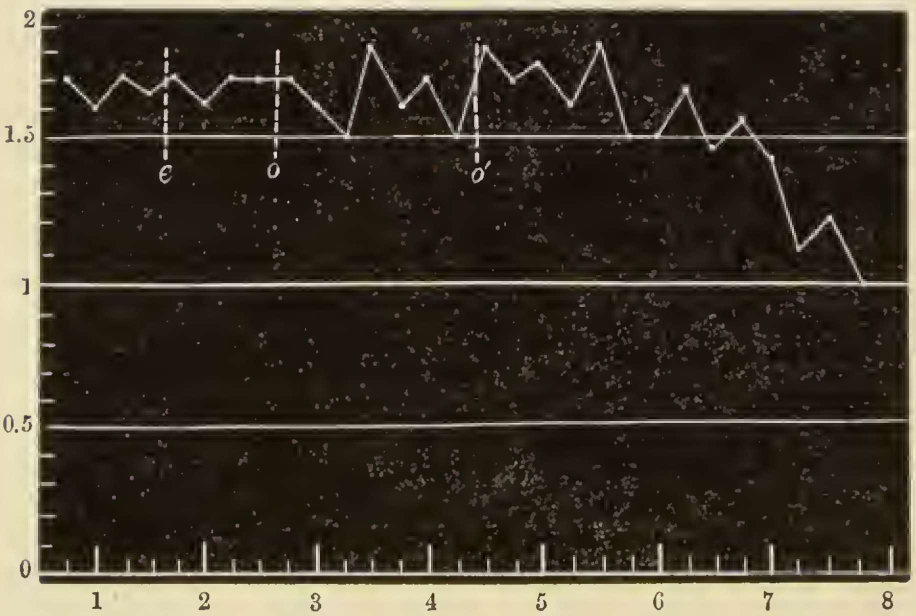
Secretion of bile before and after castor-oil. 3 cc. of bile injected into the duodenum at *b*. The same, with one ounce of castor-oil, given at *c*, and at *c′*.

AUTOPSY.—There was decided evidence of purgation in the small intestine. There was no unusual redness of the mucous membrane, save at the lower part of the duodenum.

Experiment 26. Dog that had fasted 18 hours. Weight 24.5 kilogrammes.—3 cc. bile injected into the duodenum at *b*, (Fig. 26), and 28.5 cc. castor-oil with 3 cc. bile injected at *o*, and again at *o*′.

Autopsy.—The oil had extended throughout the whole length of the small and large intestine. There was evidence of profuse purgative action, but the increased vascularity of the intestinal mucous membrane was slight.

Fig. 26.



Secretion of bile before and after castor-oil. 3 cc. bile injected into duodenum at *b*. The same with 28.5 cc. castor-oil injected at *o*, and again at *o*′.

Experiment 25 and 26 show the effect of an agent on the biliary secretion that does not excite the liver, but produces purgation by a mild irritation of the intestine. It is evident in both cases that the biliary secretion was decidedly diminished when the purgative effect became strongly marked, thus showing that purgation *per se* does nothing else than diminish the secretion of bile.

[61]

Ibid., 11: 61-86.

[Index: 623-662]

EXPERIMENTS ON THE BILIARY SECRETION OF THE DOG. By Prof. RUTHERFORD and M. VIGNAL.

SECOND SERIES.

IN the first series of our experiments we gave an account (this *Journal*, X. 253) of the action of podophyllin, colchicum, rhubarb, aloes, scammony, taraxacum, senna, gamboge, croton and castor-oil on the secretion of bile in the dog. We have now to detail the actions of a number of other substances. In these experiments we have adopted precisely the same method as in the previous ones; that is to say, we have always used dogs; these being the only animals suitable for the purpose. They had always a full meal of flesh at four o'clock in the afternoon, and the experiment was begun at nine o'clock on the following morning, so that digestion and absorption had fully taken place;—a condition that is essential for obtaining a constant secretion of bile. In all cases, irregular muscular movements were prevented by small doses of curara, it having been ascertained that these have no apparent influence on the biliary secretion, nor do they prevent the manifestation of the effects of hepatic stimulants. In consequence of the curara paralysis respiration was of course maintained artificially. As before, a glass cannula was tied in the common bile-duct, the cystic duct was clamped, and all the bile secreted was thereby compelled to flow out through the cannula into a finely graduated cc. measure, where it was constantly collected and the amount observed and recorded every fifteen minutes. Each experiment usually lasted an entire day, at the close of which the animal was killed, and the alimentary canal examined. The various substances were always injected directly into the duodenum, for the reason that, in fasting dogs, the stomach is apt to contain a large quantity of mucus that seriously interferes with the certainty of the speedy absorption of the various substances administered. We therefore had recourse to the small intestine, and we preferred the duodenal portion, in order that we might certainly bring the substance into contact with *its* mucous membrane, in case of any sympathy between it and the liver. The whole method is more fully detailed in our previous communication, but it may be well to state that in these experiments anæsthetics were not administered, because of their disturbing influence on the biliary secretion. In two of our earlier experiments we administered chloroform during the preliminary operation, but the stimulation of the liver produced thereby was so remarkable, that the animals were rendered useless for further experimentation. To avoid equivocal results, we therefore abstained from the preliminary administration of any substance other than curara.

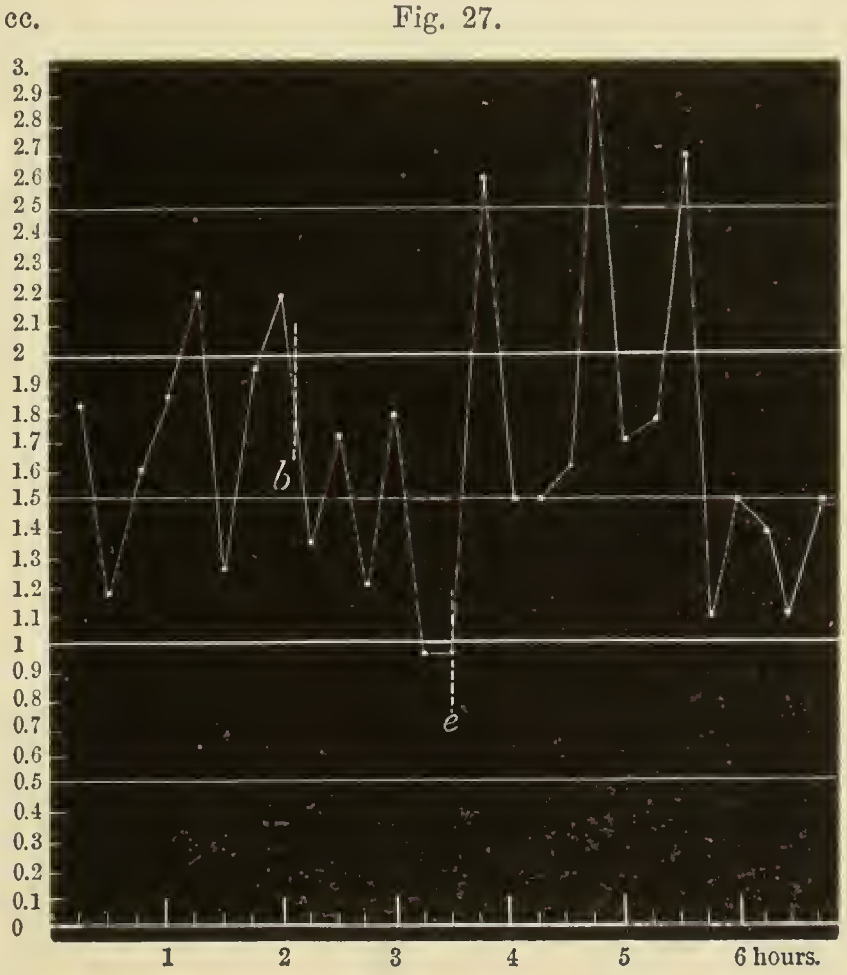
We have still confined our attention to the physiological actions of cholagogues, for it cannot be doubted that the thorough investigation of this subject is of great importance for the advance of scientific medicine.

ACTION OF "EUONYMIN."

Wood and Bache in the *United States Dispensatory* for 1869 (p. 374) state that "the precise virtues of the bark of Euonymus atropurpureus have not been determined." Mr C. A. Santos—quoted by them—describes it as "tonic, hydragogue cathartic, diuretic, and antiperiodic." Dr Tidyman informed them that he had obtained useful effects from it, as an alterative of the hepatic function. Wood and Bache conclude that "on the whole its character is somewhat uncertain; and it might well form a subject of further examination." The American "Eclectics" give "Euonymin" as a mild aperient in doses of from one to two grains. The substance used by them however is a very complex substance, only a portion of which consists of the active principle—the *true* euonymin. Mr Clothier found it to produce active purgation without griping. The substance employed in our experiments is an impure resin prepared by precipitating the tincture of euonymin with water acidulated with hydrochloric acid. It was obtained from Messrs Tilden and Co. of New York.

Experiment 27. Dog that had fasted 17 hours. Weight 19 kilogrammes. (Fig. 27.)

Fig. 27.



Secretion of bile before and after "euonymin." 2 cc. bile and 2 cc. water injected into duodenum at *b*. 5 grains of "euonymin," together with the above fluid, injected at *e*.

The irregularity in the biliary flow in this case was certainly owing to an irregularity in *secretion*, for the cannula was perfectly patent throughout the whole of the experiment. The irregularity did not consist in the bile being expelled in jets, as might have been expected had it been owing to contraction of the larger bile-ducts at intervals, but there was a rapid and steady flow for some minutes, and then for a while it flowed much more slowly. This irregularity of secretion was probably in large measure due to unusual traction upon the bile-duct and liver during the introduction

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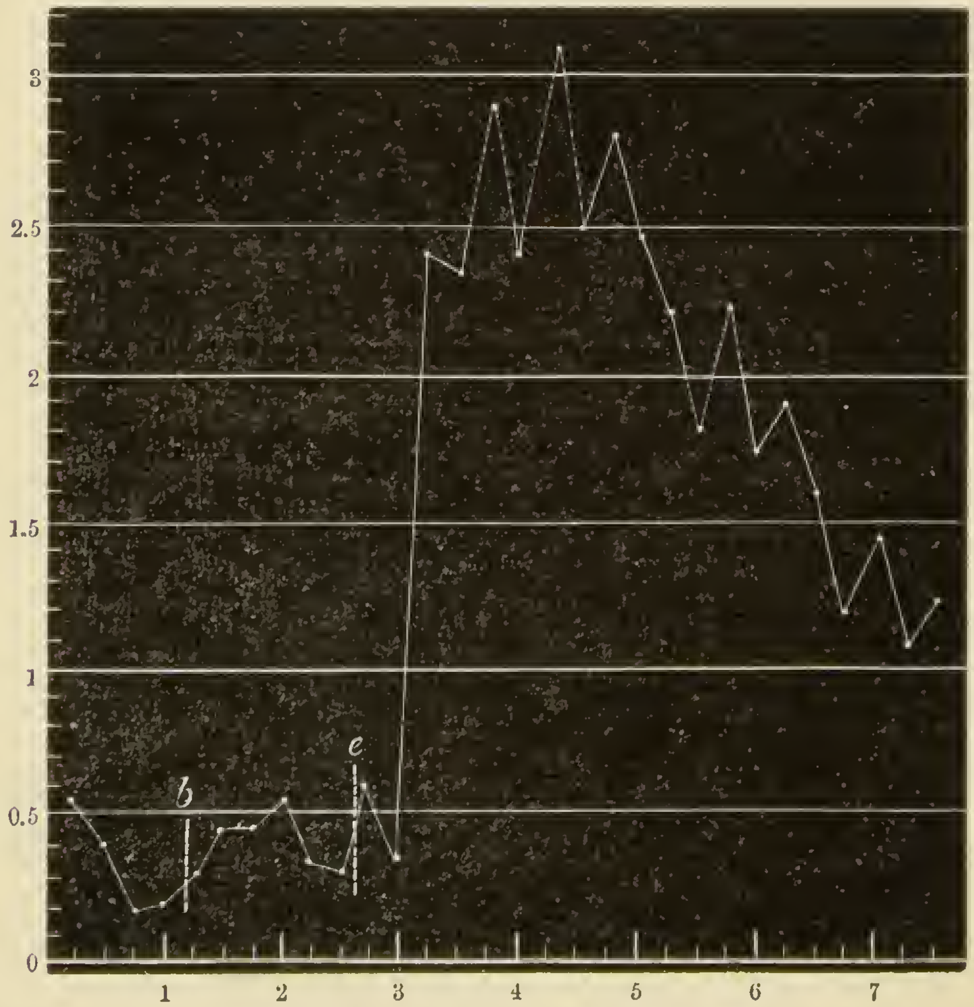
[1] Every dot in the curves in all the figures indicates the amount of bile secreted during the preceding fifteen minutes. The quantity is always expressed in cubic centimetres.

of the cannula, which in this case was much more difficult than usual. We have repeatedly observed that unless this part of the preliminary operation be conducted so as to very slightly disturb the bile-duct and its surroundings, the biliary secretion is rendered irregular. Nevertheless it is evident that in this case the "euonymin" stimulated the liver.

AUTOPSY.—There was very slight evidence of purgative action, but the mucous membrane of the upper fourth of the small intestine was much more vascular than usual.

Experiment 28. Dog that had fasted 24 hours. Weight 23.3 kilogrammes. (Fig. 28.)—The unusually long fast resulted from the animal having refused to take food on the afternoon of the day preceding the experiment. It was probably owing to this circumstance that the secretion of bile was so low at the beginning of the experiment.

Fig. 28.



Secretion of bile before and after "euonymin." 1.1 cc. bile and 3 cc. water injected into the duodenum at *b*. The same with 5 grains "euonymin" injected at *e*.

AUTOPSY.--Stomach contracted, mucous membrane normal. The "euonymin" had extended along about a third of the small intestine. The mucous membrane of the upper third was extremely vascular. Mucous flakes were scattered over the surface, and the whole appearance of the membrane reminded us of the effects of podophyllin. But notwithstanding the very obvious irritation, the intestine at this part contained only a small quantity of a watery fluid. The remainder of the intestine was dry and contracted, without any signs of irritation.

Results of Experiments with "Euonymin."—1. Five grains of "euonymin," when mixed with a small quantity of ~~boiling~~ water and placed in the duodenum, powerfully stimulated the liver[1]. 2. Coincident with the marked action of the liver there was only a slight increase of intestinal secretion. Seeing that Mr Clothier (quoted above) found "euonymin" to be an active purgative in the human subject, these experiments suggest that the purgative effect may be chiefly due to increased secretion of bile. At any rate these experiments clearly show that this substance is worthy of receiving far greater attention in practical medicine than it has done hitherto.

bile a

ACTION OF "SANGUINARIN."

Dr Wood in his excellent *Treatise on Therapeutics* (1874) states (p. 367) that "although Sanguinaria has been used more or less for so many years, we are still without any really definite knowledge of its action. Little or nothing has been added to our knowledge since the papers by Dr Tully in 1830, who stated that when given in small repeated doses it acts as a very decided cholagogue; and more recently it has been affirmed that it is also a stimulating expectorant. In full doses it is certainly a harsh emetic, and in overdoses, according to Tully, it produces with the vomiting burning at the stomach, faintness, vertigo, dimness of vision, general insensibility, coldness, extreme reduction of the force and frequency of the pulse, great prostration of the muscular strength, and sometimes a convulsive rigidity of the limbs." Dr Wood states that he has never known of its employment except as a stimulant expectorant in obstinate bronchitis. Dr Mothershead of Indianapolis (quoted in Wood and Bache's *United States Dispensatory*, 1869, p. 741) however "speaks in the strongest terms of its efficacy as an excitant of the liver, when given in alterative doses." On the other hand, Prof. Thomas, of Philadelphia (quoted by Wood and Bache, *lib. cit.*, p. 742), found the active principle sanguinarina to "have no effect of any kind directly on the liver" of man. "Sanguinarin" is however recommended by the American "Eclectics" in doses of $\frac{1}{4}$—1 grain as a hepatic alterative. The substance employed in the following experiments is a resin prepared in the same manner as euonymin (see p. 42).

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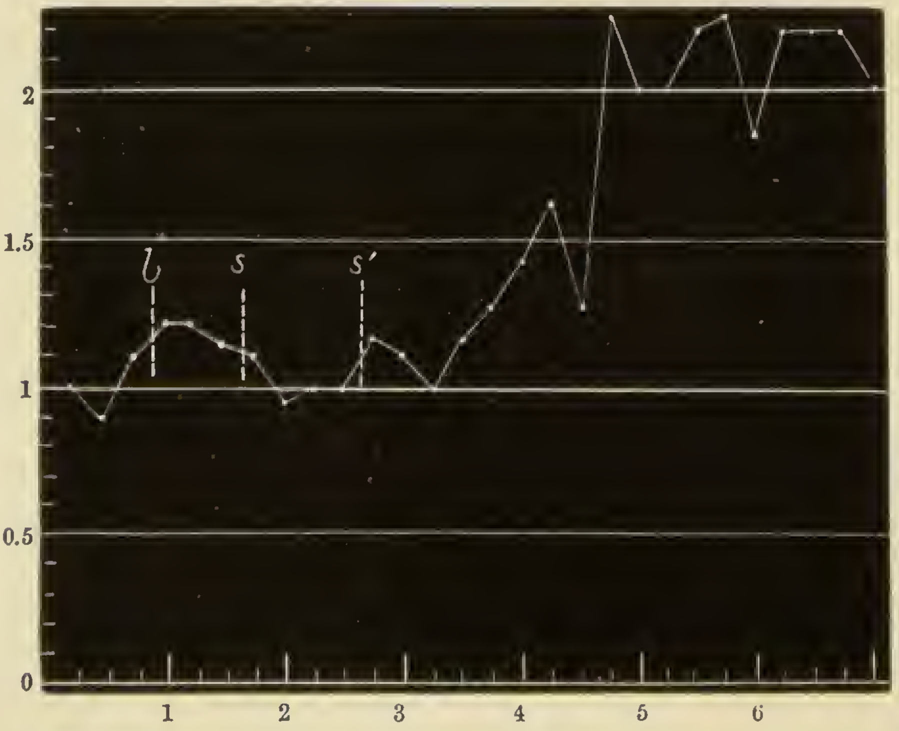
[1] The analysis of the bile secreted before and after "euonymin" was lost.

Experiment 29. Dog that had fasted 17 hours. Weight 27.7 kilogrammes. (Fig. 29.)

Fig. 29.



Secretion of bile before and after "sanguinarin." 2 cc. bile and 2.5 cc. water injected into the duodenum at *b*. 1 grain "sanguinarin" in the same fluid injected at *s*. 2 grains "sanguinarin" in the same fluid injected at *s′*.

Autopsy.—Mucous membrane of upper two-thirds of small intestine was of a clear claret colour, here and there it was marked by brownish patches of a size varying from that of a sixpence to that of a half-crown. There were 35 cc. of a thick brown fluid in the small intestine. The brown colour was apparently owing to the presence of the "sanguinarin," a substance of a brownish-red colour.

Experiment 27.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	1.82	
	1.2	
	1.6	
	1.85	
	2.2	
	1.3	
	1.95	
	2.2	
b	——	
	1.35	
	1.7	
	1.2	0.2578 cc.
	1.8	
	0.95	
	0.95	
e	——	
	2.6	
	1.5	
	1.5	
	1.6	
	2.95	0.4789 cc.
	1.7	
	1.75	
	2.7	
	1.1	
	1.5	
	1.4	
	1.1	
	1.5	

Experiment 28.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.55	
	0.4	
	0.2	
	0.21	
	0.3	
b	——	
	0.45	
	0.45	0.0708 cc.
	0.55	
	0.35	
	0.3	
e	——	
	0.6	
	0.35	
	2.4	
	2.35	
	2.9	0.4678 cc.
	2.4	
	3.1	
	2.5	
	2.8	
	2.45	
	2.25	
	1.75	
	2.25	
	1.6	
	1.85	
	1.6	
	1.2	
	1.45	
	1.1	
	1.25	

Experiment 29.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	1.0	
	0.9	
	1.1	0.1678 cc.
b	——	
	1.2	
	1.2	
	1.15	
s	——	
	1.1	
	0.95	
	1.0	
	1.0	
s′	——	
	1.15	
	1.12	
	1.0	
	1.15	
	1.25	
	1.4	
	1.6	
	1.25	
	2.22	
	2.0	0.3039 cc.
	2.0	
	2.2	
	2.22	
	1.85	
	2.2	
	2.2	
	2.2	
	2.0	

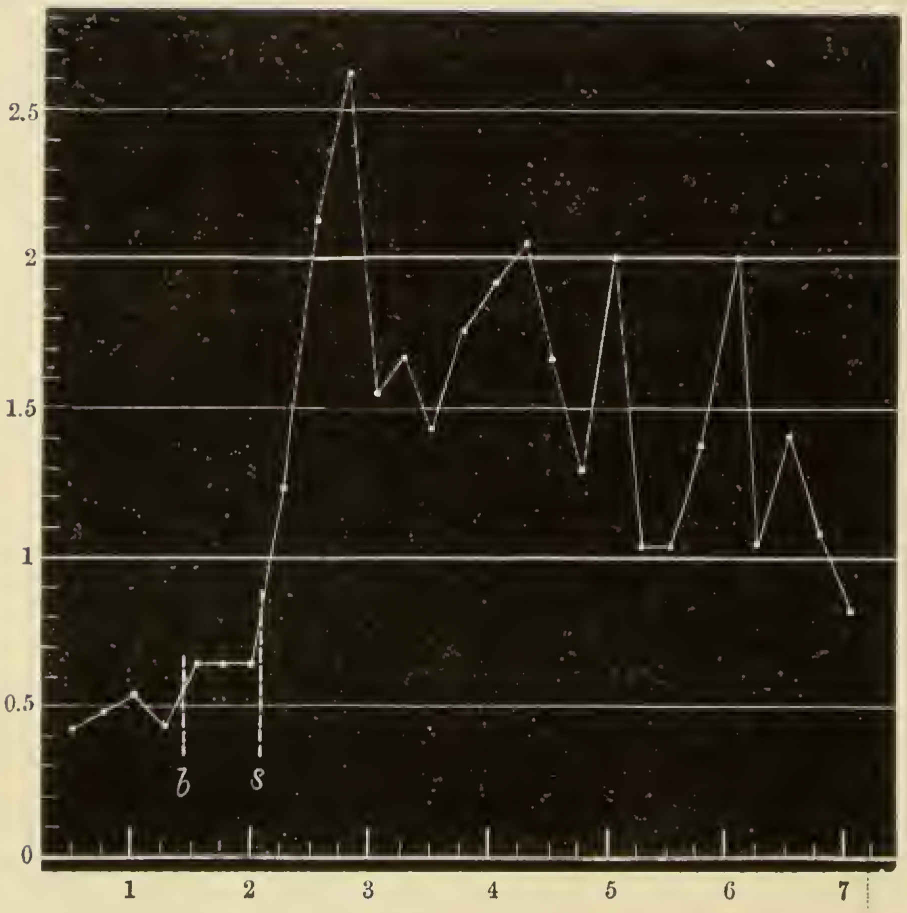
TABLE X.—*Composition of Bile before and after "Sanguinarin."*

Experiment 29.	Before.	After.
Water	90.09	91.41
Bile-acids, pigments, cholesterin, fats ...	7.38	6.57
Mucus	1.04	0.90
Ash	1.49	1.12
	100.00	100.00
Velocity of secretion per half-hour	2.4 cc.	4.25 cc.

It appears from this analysis that under the influence of "sanguinarin" the bile becomes more watery, nevertheless the velocity of secretion having been nearly doubled by this agent, it is evident that the liver secreted more biliary matter.

Experiment 30. Dog that had fasted 17 hours. Weight 20 kilogrammes. (Fig. 30.)

Fig. 30.



Secretion of bile before and after "sanguinarin." 2 cc. bile and 3 cc. water injected into the duodenum at *b*. 1 grain "sanguinarin" in the same fluid injected at *s*.

Autopsy.—Vascularity of the mucous membrane of upper half of small intestine somewhat increased. Considerable evidence of purgative action in upper half of small intestine. Contents of a viscid mucous character.

Results of Experiments with "Sanguinarin."—1. In one experiment three grains, in another experiment one grain, of "sanguinarin" when mixed with a small quantity of bile and water and placed in the duodenum powerfully stimulated the liver. 2. It rendered the bile more watery, nevertheless it caused the liver to secrete more biliary matter in a given time. 3. The secretion of the intestinal glands was slightly increased by these doses. These results show that the statements of Tully and Mothershead ought not to be treated with indifference and neglect, as they at present appear to be, in practical medicine.

ACTION OF "IRIDIN."

The root of the Iris Versicolor, or American Blue Flag, is said by Wood and Bache (*lib. cit.* p. 487) to possess cathartic, emetic and diuretic properties. The American "Eclectics" have used, under the name of "iridin" or irisin, an oleoresin obtained by precipitating a tincture of the root with water and mixing the precipitate with an equal weight of some absorbent powder. The dose of this is 1—5 grains as a purgative. "It is thought to unite cholagogue and diuretic with aperient properties" (Wood and Bache, *loc. cit.*). An anonymous writer in the *Lancet* (August 30, 1872) states that "it is gentler in its action than podophyllin, and more reliable when a slight cholagogue action is required for a lengthened period." This statement however has been generally neglected, and the substance appears to be unknown to most persons.

6

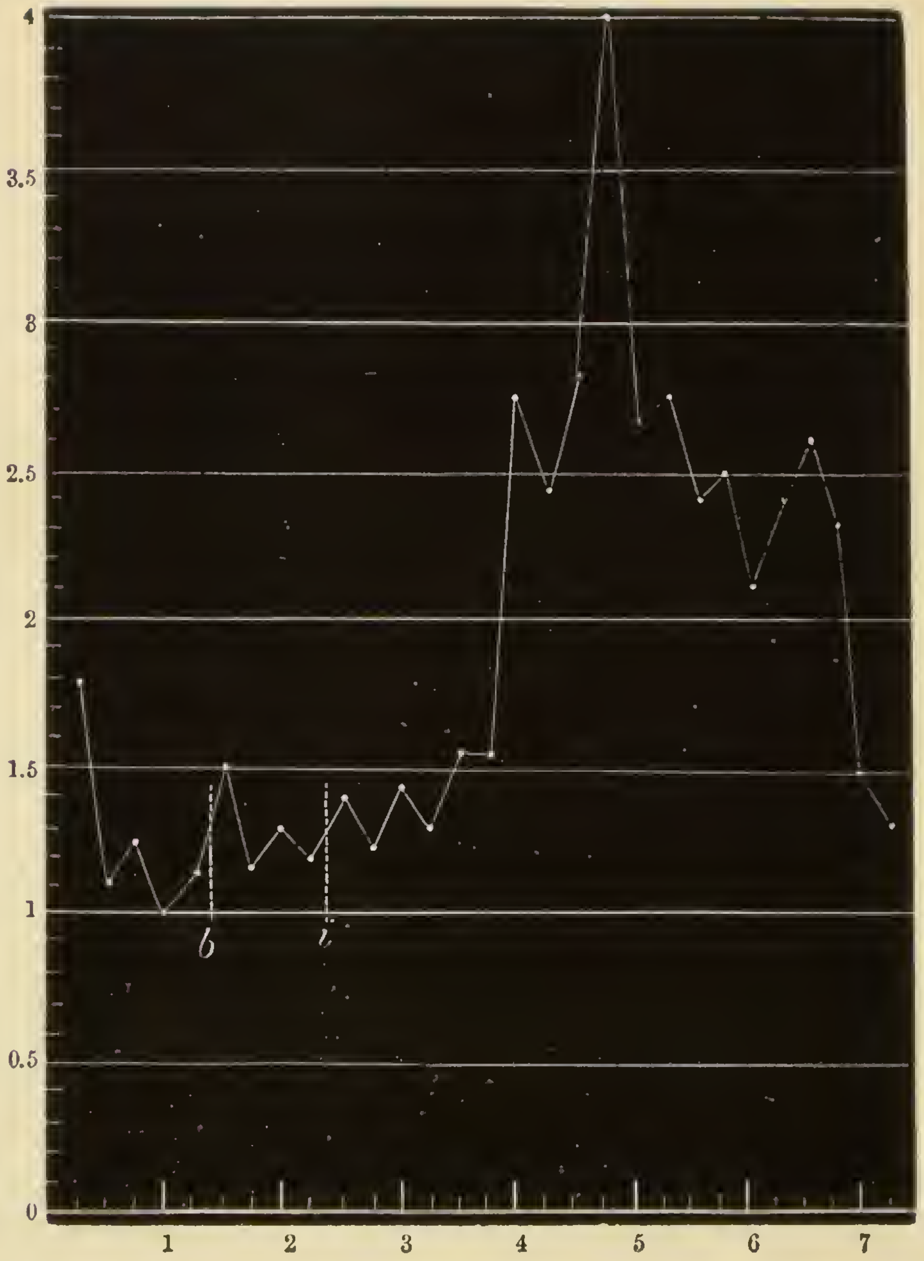
The substance employed by us is a resin prepared in the same way as euonymin (see p. 42).

Experiment 31. Dog that had fasted 17 hours. Weight 22.7 kilogrammes. (Fig. 31.)

AUTOPSY.—Stomach normal. Mucous membrane of upper two-thirds of small intestine rather more vascular than usual. This portion of the intestine contained 63 cc. of fluid, thus affording evidence of a decided purgative effect.

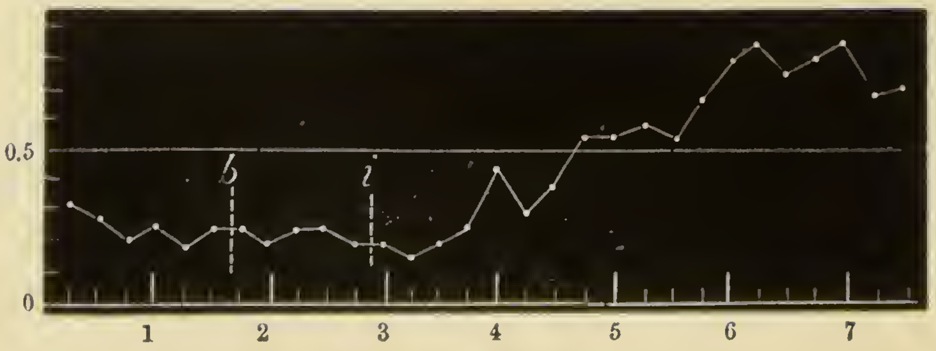
Experiment 32. Dog that had fasted 18 hours. Weight 5.4 kilogrammes. (Fig. 32.)

Fig. 31.



Secretion of bile before and after "iridin." 2 cc. bile and 3 cc. water injected into the duodenum at *b*. 5 grains "iridin" in the same fluid injected at *i*.

Fig. 32.



Secretion of bile before and after "iridin." 2 cc. bile and 2 cc. water injected into the duodenum at *b*. 5 grains "iridin" in the same fluid injected at *i*.

Experiment 30.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.41	
	0.49	
	0.52	
	0.45	0.12 cc.
b		
	0.65	
	0.65	
	0.65	
s		
	1.25	
	2.15	0.401 cc.
	2.65	
	1.55	
	1.7	
	1.45	
	1.8	
	1.9	
	2.02	
	1.7	
	1.3	
	2.0	
	1.05	
	1.05	
	1.35	
	2.0	
	1.05	
	1.4	
	1.1	
	0.8	

Experiment 31.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	1.8	
	1.1	
	1.25	
	1.0	
	1.15	
b		
	1.5	0.227 cc.
	1.16	
	1.3	
	1.2	
i		
	1.4	
	1.25	
	1.45	
	1.3	
	1.55	
	1.55	
	2.75	
	2.45	
	2.8	0.537 cc.
	4.0	
	2.65	
	2.75	
	2.4	
	2.5	
	2.1	
	2.4	
	2.6	
	2.3	
	1.5	
	1.3	

Experiment 32.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.32	
	0.3	
	0.2	
	0.25	
	0.2	
	0.25	
b		
	0.25	
	0.2	0.166 cc.
	0.25	
	0.25	
	0.2	
i		
	0.2	
	0.15	
	0.2	
	0.25	
	0.45	
	0.3	
	0.4	
	0.55	
	0.55	
	0.6	
	0.55	
	0.7	
	0.85	
	0.9	0.638 cc.
	0.8	
	0.85	
	0.9	
	0.7	
	0.75	

AUTOPSY.—Stomach normal. There was increased vascularity of the mucous membrane of nearly the whole length of the small intestine. The redness was not very marked, but it was greater than in the previous experiment. There was decided purgation, the small intestine containing 87 cc. of fluid with abundant mucous flocculi.

Results of Experiments with Iridin.—1. Five grains of iridin when mixed with a little bile and water and placed in the duodenum very powerfully stimulated the liver. It is not so powerful as large doses (four grains) of podophyllin, but it is more powerful than euonymin, as is shown by the amount of bile secreted per kilogramme of dog; the fractions for the two euonymin experiments being 0.4789 cc. and 0.4678 cc., whereas in the "iridin" experiments they are 0.537 cc. and 0.638 cc. The high fraction in the second iridin experiment probably resulted from a much smaller dog getting the same dose as in the first experiment, the smaller liver being thereby stimulated to do a proportionally greater amount of work[1]. 2. Iridin is also a decided stimulant of the intestinal glands. Judging from these experiments its irritant effects on the intestinal mucous membrane are decidedly less than those of podophyllin, while the purgative effects are greater than in the case of euonymin. The statement of the writer in the *Lancet* (above quoted) that in man "it is gentler in its action than podophyllin" is fully supported by these experiments, and there seems every reason why this substance should be removed from its present obscurity and placed in a prominent position in practical medicine.

ACTION OF "LEPTANDRIA."

"Leptandria" or "Leptandrin" is a resin prepared from the root of the American plant Leptandra Virginica or Veronica Virginica in the same manner as euonymin (see p. 42). It is a remedy that has been much lauded by the "Eclectics" as a cholagogue and tonic. As this remedy is now a good deal employed, it seemed desirable to obtain more precise information regarding its mode of action. The dose for a man is ½—3 grains three or four times daily.

Experiment 33. Dog that had fasted 18 hours. Weight 20.4 kilogrammes. (Fig. 33.)

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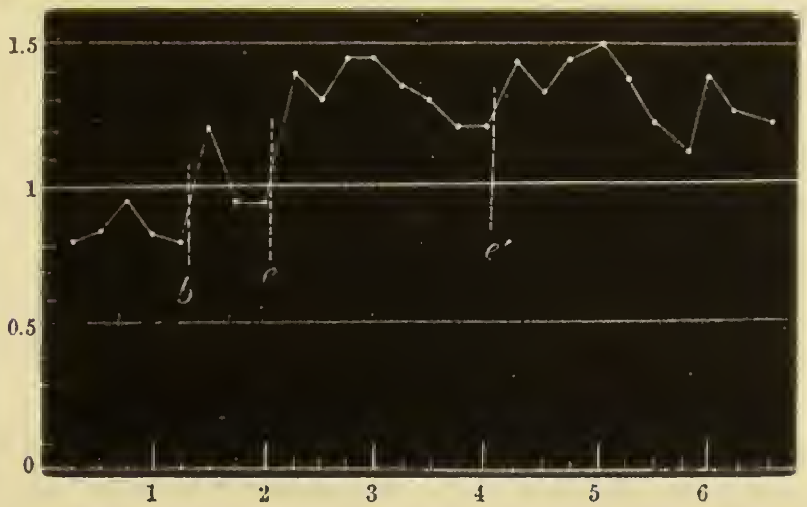
[1] The analyses of the bile secreted before and after "iridin" were lost.

Fig. 33.



Secretion of bile before and after "leptandria." 3 cc. bile and 3 cc. water injected into the duodenum at *b*. 6 grains "leptandria" in the same fluid injected at *e*. 12 grains "leptandria" in 2 cc. rectified spirit[1] and 8 cc. water injected at *e′*.

Table XI.—*Composition of the Bile before and after "Leptandria."*

Experiment 33.	Before.	After.
Water	91.34	91.41
Bile-acids, pigments, cholesterin, fats ...	6.64	6.60
Mucus	0.95	0.92
Ash	1.07	1.07
	100.00	100.00
Velocity of secretion per half-hour	1.9 cc.	2.5 cc.

It appears from this analysis that the bile secreted under the influence of leptandria retained its normal composition.

Experiment 34. Dog that had fasted 18 hours. Weight 13.1 kilogrammes. (Fig. 34.)

Autopsy.—Slightly increased vascularity of the mucous membrane of the upper half of the small intestine. There was slight purgation;—the upper half of the small intestine containing 37 cc. of a viscous fluid.

Results of Experiments with "Leptandria."—1. "Leptandria" when mixed with bile and placed in the duodenum undoubtedly

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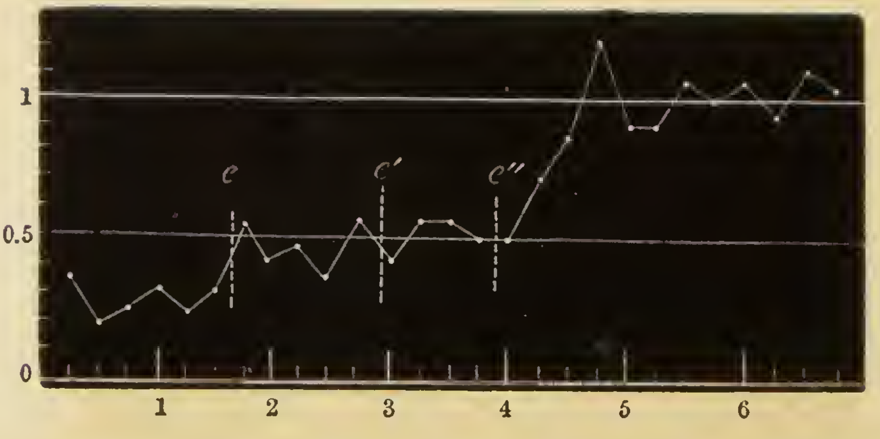
[1] We have ascertained that alcohol does not increase the secretion of bile, but rather diminishes it if the dose be large.

Fig. 34.



6 grains "leptandria" in 4 cc. water injected into the duodenum at *e*. 1½ cc. bile and 3 cc. water injected at *e′*. 12 grains "leptandria" in the same fluid injected at *e″*.

stimulates the liver, but its power is very feeble as shown by the small secretion of bile per kilogramme of dog, notwithstanding the large doses given. It excites the liver to secrete bile, having the ordinary composition. Unless the biliary solvent be present, "leptandria" produces scarcely any appreciable effect. In this respect it resembles many other resinous substances, e. g. "podophyllin." 2. It is a feeble stimulant of the intestinal glands.

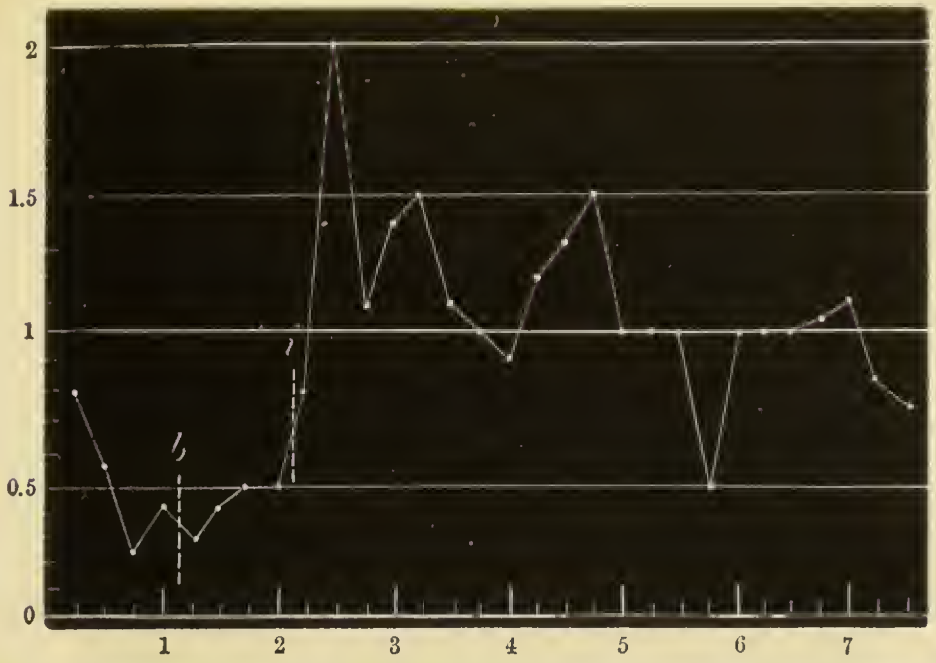
ACTION OF IPECACUAN.

As is well known, ipecacuan is regarded as almost a specific remedy in certain cases of dysentery. It is stated that it gives rise to evacuations containing a large quantity of bile. The manner in which it does this is not definitely known: some maintaining that it permits of biliary discharge by relieving spasm of the bile-ducts. The following experiments, undertaken at the desire of Sir Robert Christison, prove beyond a doubt that this substance is a powerful stimulant of the hepatic secreting apparatus.

Experiment 35. Dog that had fasted 18 hours. Weight 15 kilogrammes. (Fig. 35.)

AUTOPSY.—The ipecacuan had extended along the upper half of the small intestine, the mucous membrane of which portion was covered with thick white mucus. No purgation.

Fig. 35.



Secretion of bile before and after ipecacuan. 2 cc. bile and 3 cc. water injected into the duodenum at *b*. 60 grains ipecacuan powder in the same fluid injected at *i*.

Experiment 33.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.8	
	0.85	
	0.95	
	0.85	
	0.8	0.191 cc.
b		
	1.2	
	0.95	
	0.95	
e		
	1.4	
	1.3	
	1.45	0.272 cc.
	1.45	
	1.35	
	1.3	
	1.2	
	1.2	
e′		
	1.45	
	1.3	0.274 cc.
	1.45	
	1.5	
	1.35	
	1.2	
	1.1	
	1.4	
	1.25	
	1.2	

Experiment 34.

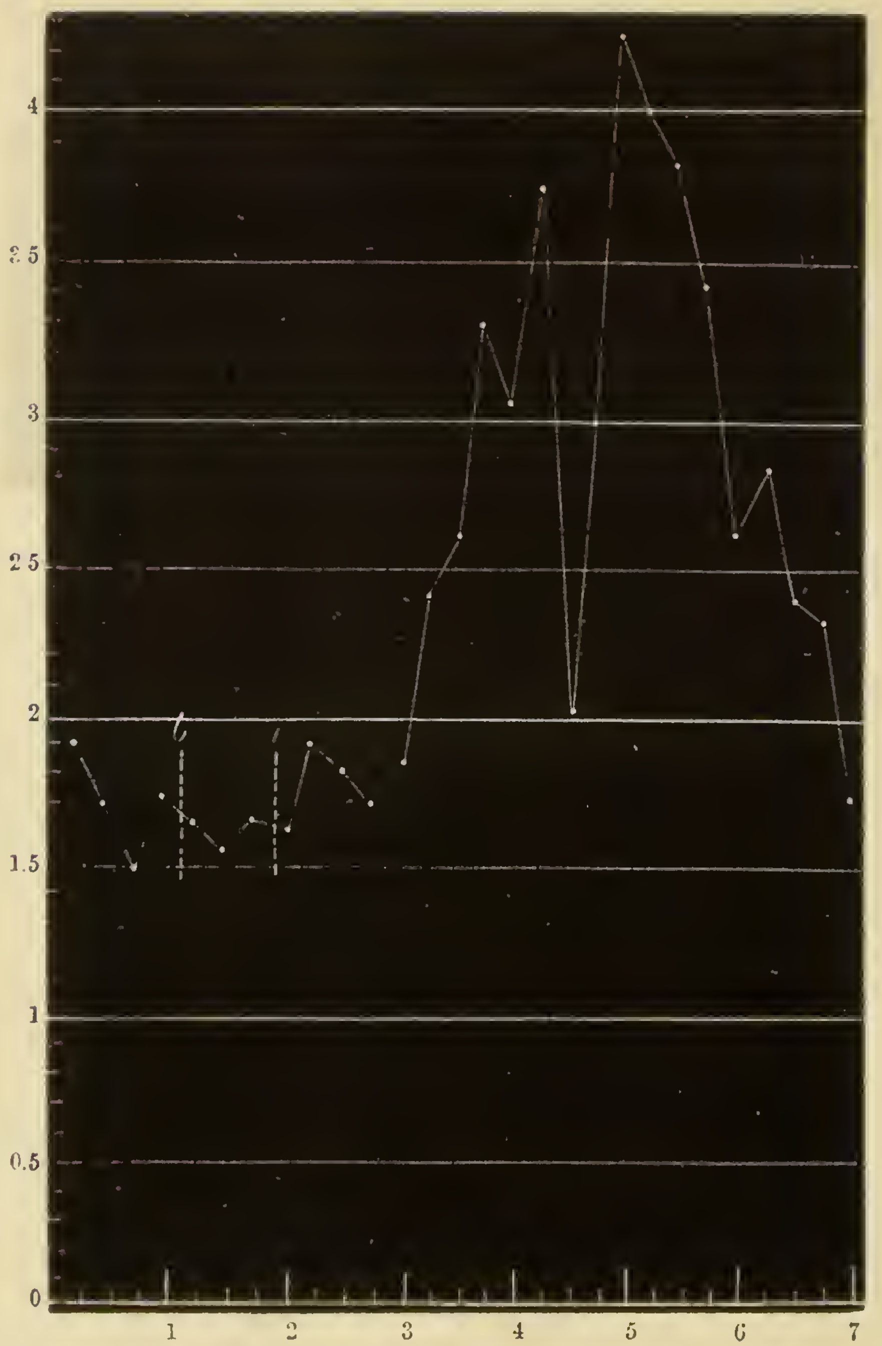
	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.35	
	0.2	
	0.25	0.0839 cc.
	0.3	
	0.25	
	0.3	
e		
	0.55	
	0.4	
	0.45	
	0.35	
	0.55	
e′		
	0.4	
	0.55	
	0.55	
	0.5	
e″		
	0.5	
	0.7	
	0.85	
	1.2	
	0.9	
	0.9	
	1.05	
	1.0	
	1.05	0.3167 cc.
	0.95	
	1.1	
	1.05	

Experiment 35.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.8	
	0.55	
	0.25	
	0.4	
b		
	0.3	0.113 cc.
	0.4	
	0.5	
	0.5	
i		
	0.8	
	2.0	0.4 cc.
	1.1	
	1.4	
	1.5	
	1.1	
	1.0	
	0.9	
	1.2	
	1.3	
	1.5	
	1.0	
	1.0	
	1.0	
	0.5	
	1.0	
	1.0	
	1.0	
	1.05	
	1.1	
	0.8	
	0.7	

Experiment 36. Dog that had fasted 18 hours. Weight 27.2 kilogrammes. (Fig. 36.)

Fig. 36.



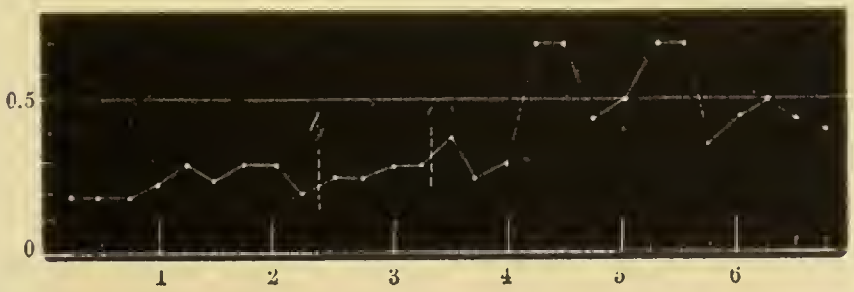
Secretion of bile before and after ipecacuan. 2 cc. bile and 5 cc. water injected into the duodenum at *b*. The same fluid with 60 grains ipecacuan powder injected at *i*.

Autopsy.—Stomach normal. The ipecacuan extended along the upper two-thirds of the small intestine, the mucous membrane of which exhibited a slight increase of vascularity, and was covered with thick mucus, but there was no purgation.

Even in much smaller doses, however, ipecacuan excites the liver, as is shown by the two following experiments.

Experiment 37. Dog that had fasted 18 hours. Weight 6.1 kilogrammes. (Fig. 37.)

Fig. 37.

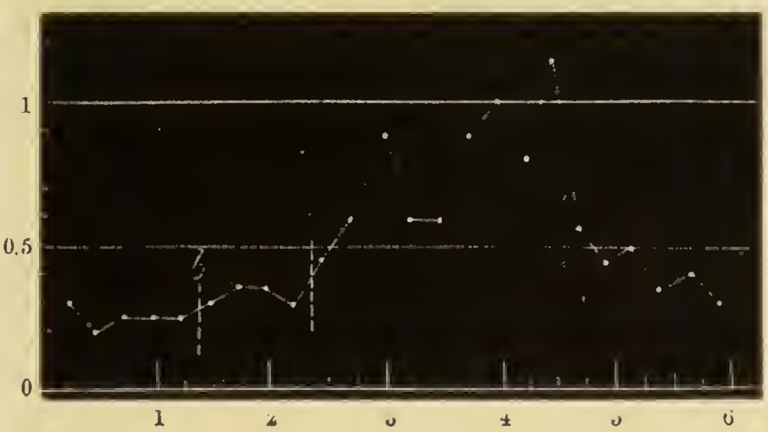


Secretion of bile before and after ipecacuan. 1.5 cc. bile and 2 cc. water injected into the duodenum at *b*. The same fluid with 3 grains of ipecacuan powder injected at *i*.

Autopsy.—Thick mucus covering the mucous membrane of upper fourth of small intestine. No purgation.

Experiment 38. Dog that had fasted 17 hours. Weight 6.8 kilogrammes. (Fig. 38.)

Fig. 38.



Secretion of bile before and after ipecacuan. 1.5 cc. bile and 2 cc. water injected into duodenum at *b*. 3 grains ipecacuan powder in the same fluid injected at *i*.

Autopsy.—The appearances of the intestine were similar to those observed in the preceding experiment.

Results of Experiments with Ipecacuan.—1. Sixty grains of powdered ipecacuan mixed with a small quantity of bile and placed in the duodenum powerfully stimulated the liver. Even three grains had an effect on a dog weighing 6.8 kilogrammes very nearly as great as the effect of sixty grains on a dog weighing 27.2 kilogrammes; the amount of bile secreted

Experiment 36.		Experiment 37.		Experiment 38.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
1.9		0.2		0.3	
1.7		0.2		0.2	
1.5		0.2		0.25	
1.7	0.24 cc.	0.25		0.25	
b ——		0.3		0.25	
1.65		0.25		*b* ——	
1.55		0.3		0.3	0.186 cc.
1.65		0.3		0.35	
i ——		0.2		0.32	
1.6		*b* ——		0.3	
1.9		0 25	0.18 cc.	*i* ——	
1.8		0.25		0.45	
1.7		0.3		0.6	
1.85		0.3		0.9	
2.4		*i* ——		0.6	
2.6		0.4		0.6	
3.3		0.25		0.9	0.506 cc.
3.05		0.3		1.0	
3.75		0.7	0.385 cc.	0.8	
2.02		0.7		1.15	
3.0	0.555 cc.	0.45		0.55	
4.25		0.5		0.45	
4.0		0.7		0.5	
3.85		0.7		0.35	
3.42		0.35		0.4	
2.6		0.45		0.3	
2.8		0.5			
2.35		0.45			
2.3		0.4			
1.7					

Composition of the Bile before and after Ipecacuan.

TABLE XII.

Experiment 36.	Before.	After.
Water	89.631	89.77
Bile-acids, pigments, cholesterin, fats ...	8.13	8.129
Mucus	1.01	0.87
Ash	1.229	1.231
	100.000	100.000
Velocity of secretion per half-hour	3.2 cc.	6.35 cc.

TABLE XIII.

Experiment 38.	Before.	After.
Water	91.32	91.51
Bile-acids, pigments, cholesterin, fats	6.73	6.73
Mucus	0.98	0.79
Ash	0.97	0.97
	100.00	100.00
Velocity of secretion per half-hour	0.65 cc.	1.9 cc.

These analyses show that, notwithstanding the acceleration of secretion by ipecacuan, the percentage amount of the special biliary constituents remains unchanged.

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per kilogramme of dog being nearly the same in both cases. 2. The bile secreted under its influence was of normal composition as regards the biliary matter proper. 3. No purgative effect was produced, but there was an increased secretion of mucus in the small intestine. The composition of the bile did not afford any evidence of an increased secretion of mucus having taken place from the glands of the bile-ducts.

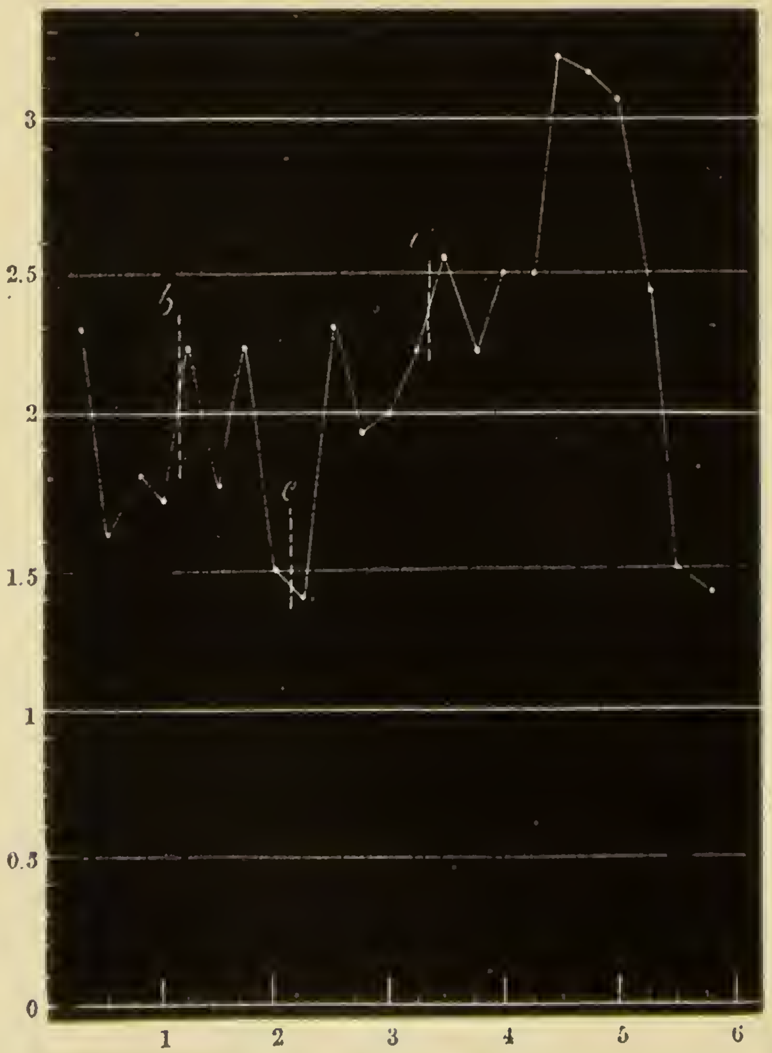
The increased biliary flow that followed ipecacuan could not in these experiments be ascribed to any relaxation of "spasm of the bile-ducts," for that no such thing existed was clearly shown by the free flow of the bile before the substance was given. Nor could it be owing to contraction of the gall-bladder, for the cystic duct was clamped. Nor can it be ascribed to contraction of the bile-ducts, for the increased flow was far too prolonged to be attributable to any such cause. It is therefore certain that this substance, like the others, has the power of stimulating the *secreting* apparatus of the liver. This being now proved as regards the dog, it can scarcely be doubted that the *modus operandi* is the same in man. The results of these experiments will therefore lead to new speculations regarding the pathology of dysentery; for *every step towards greater accuracy of knowledge regarding the* modus operandi *of any therapeutic agent is certainly calculated to advance our knowledge of the true nature of the pathological condition that is relieved or cured by it.*

ACTION OF COLOCYNTH.

Colocynth and jalap are substances whose action on the biliary secretion of the dog has already been investigated by Röhrig (*Stricker's Jahrbücher*, 1873, p. 240). According to that observer croton oil is a powerful cholagogue, and colocynth and jalap stand near it in importance. We have already pointed out the faultiness of Röhrig's method, and have shown (this *Journal*, Vol. x. p. 259) that croton oil is scarcely worthy of being classed amongst cholagogues. It seemed therefore desirable that we should experiment with colocynth and jalap in order to have results comparable with our experiments on other substances.

Experiment 39. Dog that had fasted 16 hours. Weight 26.3 kilogrammes. (Fig. 39.)

Fig. 39.

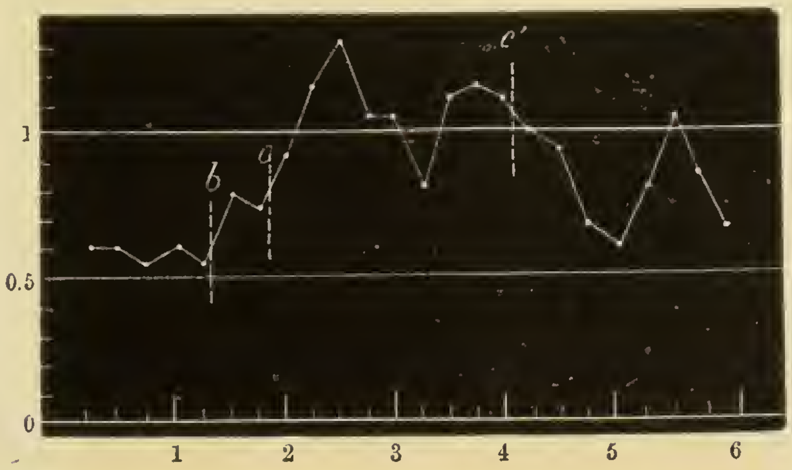


Secretion of bile before and after colocynth. 2 cc. bile and 2 cc. water injected into the duodenum at *b*. The same fluid with 7 grains of powdered colocynth pulp injected at *c*. The same dose repeated at *c′*.

AUTOPSY.—Gastric mucous membrane very vascular. The mucous membrane of the small intestine was intensely vascular throughout its entire length. There was evidence of powerful purgation,—the small intestine containing 82 cc. of fluid.

Experiment 40. Dog that had fasted 16 hours. Weight 16.3 kilogrammes. (Fig. 40.)

Fig. 40.



Secretion of bile before and after colocynth. 3 cc. bile and 3 cc. water injected into the duodenum at b. The same repeated at c′.

b. The same with 7 grains Colocynth gi
at c.

AUTOPSY.—There was increased vascularity throughout the whole length of the mucous membrane of the small intestine, especially marked in the upper part. There was considerable evidence of purgation.

Composition of the Bile before and after Colocynth.

TABLE XIV.

Experiment 39.	Before.	After.
Water	92.99	94.13
Bile-acids, pigments, cholesterin, fats ...	5.49	4.70
Mucus	0.90	0.70
Ash	0.62	0.47
	100.00	100.00
Velocity of secretion per half-hour	3.4 cc.	6.35 cc.

TABLE XV.

Experiment 40.	Before.	After.
Water	91.48	91.72
Bile-acids, pigments, cholesterin, fats ...	6.85	6.69
Mucus	0.83	0.77
Ash	0.84	0.82
	100.00	100.00
Velocity of secretion per half-hour	1.15 cc.	2.35 cc.

These analyses show that colocynth renders the bile more watery, although it at the same time increases the secretion of the special biliary matters.

In Exp. 40, the pulse became very weak towards the close of the experiment, and it may be that this weakness rendered the effect of the colocynth upon the liver less than it otherwise might have been. Be this as it may, we did not think it necessary to perform another experiment, for the first experiment with this substance may be regarded as sufficient.

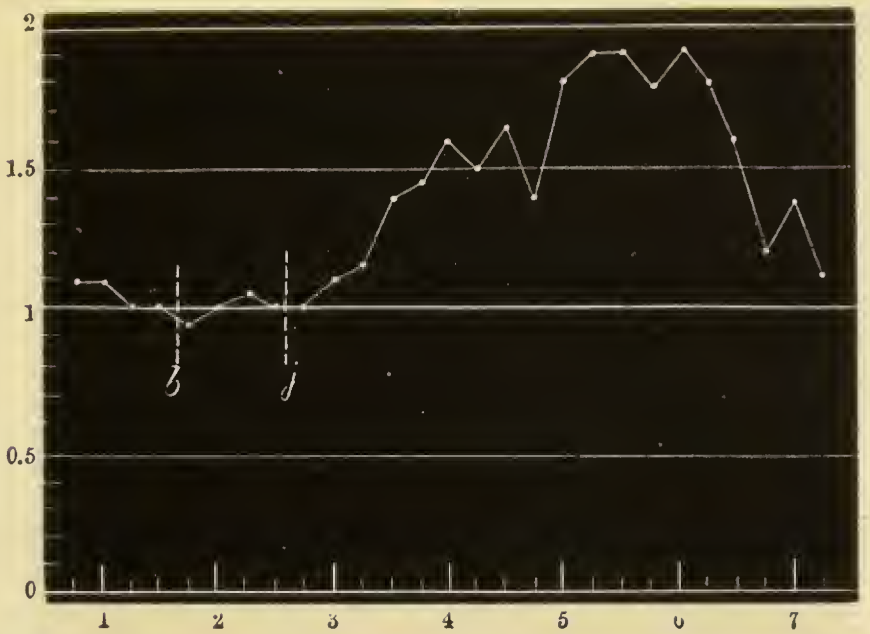
Results of the Experiments with Colocynth.—1. Colocynth is a hepatic stimulant of considerable power. It renders the bile more watery but nevertheless increases the secretion of biliary matter. 2. It is also a powerful stimulant of the intestinal glands.

ACTION OF JALAP.

Experiment 41. Dog that had fasted 17 hours. Weight 25 kilogrammes. (Fig. 41.)

AUTOPSY.—The jalap had extended along about four-fifths of the small intestine, the mucous membrane of which was more vascular than usual, especially so at the lower part of the duodenum. The purgative effect was considerable—there being 64 cc. of fluid in the intestine. The fluid was of a very watery character.

Fig. 41.



Secretion of bile before and after jalap. 2.5 cc. bile and 2.5 cc. water injected into the duodenum at *b*. 30 grains of jalap powder in the same fluid injected at *j*.

Experiment 39.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	2.3	
	1.6	
	1.8	
b	——	
	1.7	
	2.2	0.2908 cc.
	1.75	
	2.2	
	1.5	
c	——	
	1.4	
	2.3	
	1.95	
	2.0	
	2.2	
c′	——	
	2.55	
	2.2	
	2.5	
	2.5	0.452 cc.
	3.2	
	3.15	
	3.05	
	2.45	
	1.5	
	1.4	

Experiment 40.

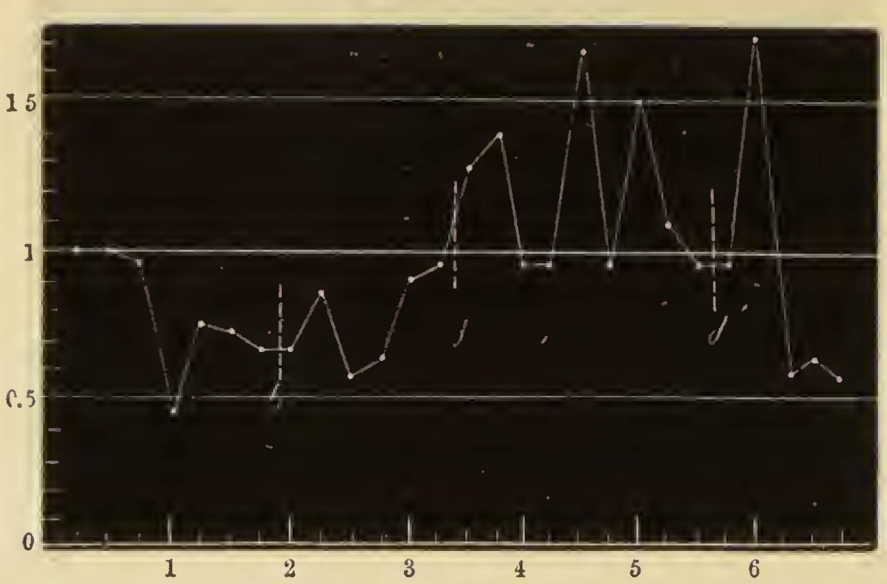
	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.6	
	0.6	
	0.55	
	0.6	0.165 cc.
	0.55	
b	——	
	0.8	
	0.75	
c	——	
	0.9	
	1.15	0.279 cc.
	1.3	
	1.05	
	1.05	
	0.8	
	1.1	
	1.15	
	1.1	
c′	——	
	1.0	
	0.95	
	0.65	
	0.6	
	0.8	
	1.05	
	0.85	
	0.65	

Experiment 41.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	1.1	
	1.1	
	1.0	
	1.0	
b	——	
	0.95	0.16 cc.
	1.0	
	1.05	
	1.0	
j	——	
	1.0	
	1.1	
	1.15	
	1.4	
	1.45	
	1.6	
	1.5	
	1.65	
	1.4	
	1.8	
	1.9	
	1.9	0.296 cc.
	1.8	
	1.9	
	1.8	
	1.6	
	1.2	
	1.4	
	1.1	

Experiment 42. Dog that had fasted 20 hours. Weight 11.8 kilogrammes. (Fig. 42.)

Fig. 42.



Secretion of bile before and after jalap. 3 cc. water and 2 cc. bile injected into the duodenum. 20 grains jalap powder in the same fluid injected at *j*, and again at *j′*.

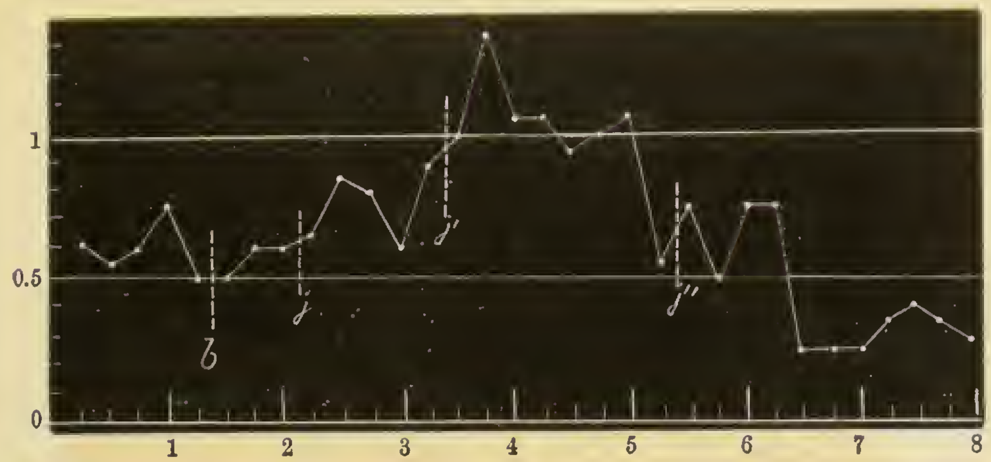
AUTOPSY.—Profuse purgative action throughout the whole extent of intestine. Vascularity of mucous membrane of small intestine somewhat increased, most marked in the duodenum.

The rapid fall in the bile-secretion towards the close of this experiment probably resulted from the purgation. It is to be noted that in *Exp.* 42, a *larger* dose of jalap was given (40 grains) to a dog less than half the size of the subject of *Exp.* 41. This is doubtless the cause of the greater effect on the liver and on the intestinal glands in *Exp.* 42. The effect of a still larger dose in a dog of nearly the same weight as No. 42 is instructive. (See Fig. 43.)

Experiment 43. Dog that had fasted 22 hours. Weight 12.3 kilogrammes. (Fig. 43.)

AUTOPSY. 20 cc. of fluid had been injected into the duodenum, much of which had probably been absorbed; the small intestine, however, contained in its upper third 117 cc. of watery fluid, showing that a profuse purgative action was taking place. The jalap had extended along only a third of the small intestine.

Fig. 43.



Secretion of bile before and after jalap. 2 cc. bile and 3 cc. water injected into duodenum at *b*. 20 grains jalap powder in the same fluid injected at *j*, *j′*, and *j″*.

The fall of the bile-secretion towards the close of the experiment is only another illustration of the fact often witnessed by us—*that severe purgation diminishes the secretion of bile.*

Composition of the Bile before and after Jalap.

TABLE XVI.

Experiment 41.	Before.	After.
Water	89.31	89.75
Bile-acids, pigments, cholesterin, fats ...	8.41	8.05
Mucus	0.93	0.87
Ash	1.35	1.33
	100.00	100.00
Velocity of secretion per half-hour	2.1 cc.	3.7 cc.

TABLE XVII.

Experiment 42.	Before.	After.
Water	87.91	88.19
Bile-acids, pigments, cholesterin, fats ...	9.94	9.87
Mucus	0.73	0.52
Ash	1.42	1.42
	100.00	100.00
Velocity of secretion per half-hour	1.4 cc.	2.55 cc.

Experiment 43.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	1.0	
	1.0	
	0.95	
	0.45	
	0.75	
	0.7	
	0.65	
b		
	0.65	
	0.85	
	0.55	0.254 cc.
	0.6	
	0.9	
	0.95	
j		
	1.25	
	1.35	
	0.95	
	0.95	
	1.65	0.436 cc.
	0.95	
	1.5	
	1.05	
	0.95	
j′		
	0.95	
	1.75	
	0.55	
	0.6	
	0.55	

Experiment 44.

	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
	cc.	
	0.6	
	0.55	
	0.6	
	0.75	
	0.5	0.178 cc.
b		
	0.5	
	0.6	
	0.6	
j		
	0.65	
	0.85	
	0.8	
	0.6	
	0.9	
j′		
	1.0	
	1.35	0.357 cc.
	1.05	
	1.05	
	0.95	
	1.0	
	1.05	
	0.55	
j″		
	0.75	
	0.5	
	0.75	
	0.75	
	0.25	
	0.25	
	0.25	
	0.35	0.113 cc.
	0.4	
	0.35	
	0.3	

Results of Experiments with Jalap.—1. Jalap is a hepatic stimulant of considerable power. It renders the bile more watery, but at the same time increases the secretion of biliary matter. 2. Its effect on the liver is however far less notable than its effects on the intestinal glands. Its hydrogogue cathartic effects on these were fully manifested in these experiments.

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"Third Series"

Ibid., pp 623 — 662

[Ends: "To be continued"
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the "*Third Period*"]

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